Factors affecting outcome of non-surgical root canal treatment

A thesis submitted by

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Abstract

Aims

To investigate the probability of success and influencing factors for primary and secondary root-canal-treatments using two outcomes (absence of apical periodontitis [AbAP] and tooth survival [TS]).

Methodology

Part 1 involved meta-analyses of previous outcome data selected, extracted and agreed by three reviewers. Statistical heterogeneities and their sources were investigated using meta-regression.

Part 2 involved prospective follow-up of upto four years of root-canal-treatments in an Eastman cohort. AbAP by root was estimated and the associated prognostic factors were investigated using logistic regression. TS was estimated and prognostic factors investigated using Cox regression. Potential interactions between factors and primary/secondary root-canal-treatment were explored. Clustering effects within patients were adjusted in all models using robust standard error.

Results

Meta-analyses revealed the pooled AbAP associated with primary and secondary root-canal-treatments were 75%(70%–80%) and 77%(61%–88%), respectively. Three (periapical lesion, root filling extent, quality of restoration) of the four prognostic factors identified for primary root-canal-treatment also had significant influence on secondary root-canal-treatment.

Prospective data revealed insignificant difference in AbAP between primary (83%[81%–85%]) and secondary (80%[78%–82%]) treatment. The influence of 11 prognostic factors (including 3 from meta-analyses) was the same for both treatments except, “EDTA-as-an-additional-irrigant”; it had no effect on primary treatment but significantly increased success of secondary treatment (OR=2.3[1.4–3.8]).

Meta-analysis revealed the pooled TS probabilities (2–10 year) ranged from 72–86%; with 4 prognostic factors (Tooth type & function, restoration, proximal contacts).

Prospective data found that 4-year TS after primary treatment (95.4%[94%–97%]) or secondary treatment (95.3%[94%–97%]) were similar; with fourteen prognostic factors including 2 from the meta-analysis.

Conclusions

Meta-analyses and prospective data were in concordance. Success based on AbAP or tooth-survival, and the prognostic factors for primary and secondary root-canal-treatment were similar. Only “EDTA-as-an-additional-irrigant” had different effects on the two treatments. This study revealed some new prognostic factors.

DECLARATION

I hereby certify that the work embodied in this thesis is entirely the result of my own investigations. This research project has not been submitted either in part or in full for a degree or diploma to this or any other University or examination board elsewhere.

Yuan Ling Ng

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Chapter 1

Introduction

1.0 Justification for the study

Periapical disease is an inflammatory response around root canal termini in response to intra-radicular bacterial infection. It can be prevented (in the case of pulp inflammation) or resolved (in the case of pulp infection) by root canal treatment. The scientific basis and validity of root canal treatment was challenged early in its history during the "Focal infection era" (Rosenow 1909). The procedure virtually disappeared from practice and the discipline was removed from many undergraduate curricula (Kirk & Antony 1930). The practice was sustained by a few clinicians with the foresight to see their errors. Their confidence in the procedure could only have been based on personal experience. These practitioners (Hinman 1921, Blayney 1922, Grove 1923, Rhein 1926, Puterbaugh 1926, Coolidge 1927, Buchbinder 1936, Auerbach 1938) carried out the procedures assiduously, recorded their details as well as monitoring their outcomes clinically and radiographically. By 1928, it would appear that the modern principles were established and accepted; even that the judgements should be made on their outcome from a proper cohort of studied patients (Halls 1928). Despite this early endeavour and adherence to principles by a visionary few, the prevalence of untreated periapical disease, root canal treatment and in particular that performed sub-optimally with persistent periapical disease remains depressingly high (Eriksen *et al.* 2002). This, in spite of advances in the understanding of biological aetiology of periapical disease, rationale for root canal treatment, and improvement in materials, equipment and techniques for treatment delivery. The problem has posed a substantial economic and manpower burden to modern society (Figdor 2002). Since 1992, over £43 million has been spent each year on root canal treatment in the general dental services of the National Health Service in UK (Dental Practice Board 2005). Up-to-date guidelines & standards (British Endodontic Society 1983, European Society of Endodontology 1994, 2006, Canadian academy of Endodontics 2006) help guide clinicians towards better outcomes, but some of the principles are based on microbiological load reduction rather, than clinical outcome studies.

Although randomised controlled trials are regarded as the gold standard in clinical research, the majority of previous studies on root canal treatment outcome are retrospective surveys. Numerous studies have analysed the influence of a variety of factors on the outcome of primary root canal treatment, but only a small proportion has investigated prognostic factors for root canal re-treatment (secondary root canal treatment). Using clinical and radiographic signs of periapical disease as the outcome measure, the reported success rates range widely from 31% to 100% for primary (first time) root canal treatment and from 28% to 90% for secondary (repeat) root canal treatment. Direct comparisons between studies are complicated by differences in study design, criteria for success and uncontrolled combinations of pre-operative, intra-operative and post-operative factors. Despite this, it is intuitively evident that certain factors have been frequently investigated and have a strong influence on outcome; these include the pre-operative status of the root canal, presence of the periapical lesion, culture result prior to obturation, previous root canal treatment, the apical extent of root filling, and the presence of an adequate coronal restoration. Very few studies have dissected the influence of various aspects of the treatment procedures on the treatment outcome. It would be clinically valuable to have detailed insight into the influence of prognostic factors of a treatment procedure to enable improvements in success as well as to aid the decision-making process in selection of treatment options. Such considerations have been confounded by a lack of standard outcome measure.

Classically root canal treatment procedures are measured by signs and symptoms of periapical healing but alternative treatments, such as implants focus on survival of restorations. This has prompted the recommendation by the American Association of Endodontists of adopting revised definitions of success (Friedman & Mor 2004). Since the turn of the millennium, a number of studies (Lazarski *et al*. 2001, Caplan *et al.* 2002, Salehrabi & Rotstein 2004, Stoll *et al*. 2005, Lumley *et al*. 2008) have reported on the survival of teeth after root canal treatment. The characteristics of these studies vary enormously. When analysing the effect of potential influencing factors on treatment outcome, appropriate statistical methods have not been used in most previous studies. The chi-squared test was the most commonly used statistic but it does not allow several independent variables to be considered simultaneously. Although regression models were used in some studies, the hierarchical nature of the data was not accounted for.

The shift from clinical practice driven by authoritative synthesis to one driven by a systematic evidence-based approach (Cochrane Oral Health Group in June 1994 http://www.ohg.cochrane.org/about.html, Sackett *et al.* 1996) encourages clinicians and researchers to produce better quality evidence for root canal treatment. This shift, resulted in a surge of systematic reviews on this subject (Hepworth & Friedman 1997, Basmadjian-Charles *et al*. 2001, Lewsey *et al*. 2001, Kojima *et al*. 2004, Paik *et al*. 2004, Sathorn *et al*. 2005b, Schaeffer *et al*. 2005, Torabinejad *et al*. 2005, Del Fabbro *et al*. 2007, Figini *et al*. 2007, Peng *et al*. 2007, Stavropoulou & Koidis 2007, Torabinejad *et al*. 2007); the majority were published after the beginning of this PhD thesis in Jan 2004. Most have investigated specific prognostic factors for the resolution of clinical and radiographic signs of periapical disease, including: vitality of teeth (Lewsey *et al*. 2001, Kojima *et al*. 2004), periapical status (Basmadjian-Charles *et al*. 2001), apical extent of root filling (Kojima *et al*. 2004, Schaeffer *et al*. 2005), number of treatment visits (Sathorn *et al*. 2005, Figini *et al*. 2007), and cold lateral versus warm compaction of gutta-percha root fillings (Peng *et al*. 2007). Only Paik *et al*. (2004) assessed the level of evidence available for the outcome of secondary root canal treatment.

Lately, the high probability of survival of osseointegrated dental implants has provided an alternative approach for the management of endodontic problems, through extraction and replacement of teeth. Thus the outcome of primary and secondary treatment have been compared in systematic reviews with their competing treatment options for previously untreated teeth (Torabinejad *et al*. 2007) and previously treated teeth (Del Fabbro *et al*. 2007), respectively. Torabinejad *et al*. (2007) compared the long-term survival, psycho-social, and economic outcomes between primary treatment and restoration versus extraction and replacement with implant-supported crowns, fixed partial dentures, or extraction without tooth replacement.

Considering the diversity of the retrospectively collected published data, there was a need to carry out a thorough systematic review using an approach accounting for the heterogeneity of observational data. The results of such a review would help inform the design of future prospective studies, adopting more comprehensive data recording to investigate the influence of treatment factors. Furthermore, prospective studies could adopt multiple outcome measures, using appropriate methods for analysis of the complex datasets.

The endodontic literature was systematically and critically reviewed and synthesised to establish the knowledge base pertinent to the problem. This is classified and presented below.

1.1 Definition of root canal treatment

"Endodontology is concerned with the study of the form, function and health of, injuries to and diseases of the dental pulp and periradicular region, their prevention and treatment; the principle of disease being apical periodontitis, caused by infection" (European Society of Endodontology 2006). Root canal treatment is a "non-surgical" approach used to treat two distinct endodontic disease entities: (1) "extirpated" vital, but irreversibly inflamed pulp, where the goal is to maintain existing periapical health and thus prevent periapical disease; or (2) the non-vital or dying, infected pulp, associated with apical periodontitis. Root canal "retreatment" is used to treat persistent "post-treatment" apical periodontitis after prior failed root canal treatment. The goal of treatment for apical periodontitis is to restore the periradicular tissues back to health. The overall goal of root canal treatment is therefore to prevent or treat periapical disease (European Society of Endodontology 2006).

The first time treatment of pulpal or periapical inflammation is described as primary root canal treatment, whilst repeated treatment of persistent disease is described as secondary root canal treatment.

1.2 Biological distinctness of disease entities requiring root canal treatment

The distinctly described disease entities above are in fact stages at the extremes of a continuum. The dental pulp responds to microbiological, mechanical, thermal or chemical insults with a localised inflammatory response followed by occlusion of involved dentinal tubules and focal secretion of tertiary reactionary or reparative dentine adjacent to the site of injury [Kuttler 1959, Massler & Pawlak 1977, Morrant 1977, Langeland 1987, Murray *et al.* 2000, About *et al.* 2001]. Vitality of the odontoblast cell layer [About *et al.* 2001] as well as the effective elimination and prevention of a possible microbial challenge [Hume & Massey1990] dictate the successful repair of damaged dentine matrix. This defence is mediated through an increase of sub-odontoblastic progenitor cells and a consolidation of the barrier between the pulp and the irritant. Survival of the crucial odontoblast cells is influenced by residual dentine thickness and to a lesser degree by the type of restorative material [Murray *et al.* 2000, About *et al.* 2001]. When the pulp is breached, lost odontoblasts, are replaced by migration and differentiation of the progenitor cells into odontoblast-like cells which become responsible for secretion of the reparative dentine matrix [Smith & Lesot 2001]. In case of persistent bacterial challenge from untreated caries, exposed dentine or pulp, the inflammation persists and becomes chronic, resulting in suppurative inflammation, abscess formation (partial pulpal necrosis) and ultimately total pulpal necrosis [Kakehashi *et al.* 1965]. Total necrosis of the pulp may also occur without infection when the blood supply is severed following acute traumatic injury to the tooth and supporting tissues [Andreasen *et al.* 1995]. In such cases, the periapical tissues may remain healthy as long as bacteria do not enter [Bergenholtz 1974, Sundqvist 1976].

With the onset of infection and its apical progression into the root canal system, an initial acute non-specific inflammatory response sets in within the periradicular tissues adjacent to canal exits. In cases of progressive pulp necrosis, this takes place well in advance of total pulpal necrosis [Langeland 1987, Yamasaki *et al.* 1994]. At this stage, bone destruction is not visible radiographically but there maybe slight widening of the periodontal ligament space around the root apex. In the absence of treatment intervention, bone destruction would progress and become radiographically detectable as a radiolucent lesion and the inflammation may make a transition to an acute abscess or a chronic state [Nair 1997]; the latter is clinically classified as chronic apical periodontitis. The area of bone destruction has been shown in an animal model to increase with time with a rapid phase between 7 and 15 days and stabilisation after 30 days [Stashenko *et al.* 1992]. There is a concomitant increase in the proportion of anaerobic bacteria in the root canal [Stashenko *et al.* 1992]. The ultimate extent of bone destruction is a function of the number of bacterial cells and species present in the root canal system [Sundqvist 1976] and their interaction with the host [Stashenko *et al.* 1992]. The clinical presentation of chronic apical periodontitis ranges from absence of signs and symptoms (chronic apical periodontitis) to discharging sinus (chronic suppurative apical periodontitis) and presence of pain and swelling (acute exacerbation of a chronic lesion). The variation in presentation probably depends on the nature of interaction between host and bacterial challenge but this relationship has not been fully elucidated. Deficiency in function and quantity of polymorphonuclear neutrophils (PMNs) may result in susceptibility to severe infection and development of larger periapical lesions in both animals (Kawashima *et al.* 1999) and humans (Majorana *et al.* 1999). Conversely, systemic administration of a biologic response modifier to increase PMN production, reduced periapical bone destruction by 40% (Stashenko *et al.* 1995). These findings however, were not fully supported by observations in patients with diabetes mellitus. It is a metabolic disease associated with altered or impaired PMN function (Iacono *et al.* 1985, Sawant 1993, Delamaire *et al.* 1997, Karima *et al.* 2005) and these patients were found to have a disproportionately high percentage of clinically severe pulpal infections (Ueta *et al.* 1993). However, the diagnosis of diabetes had no association with prevalence of periradicular lesion (Falk *et al.* 1989, Britto *et al.* 2003). This was corroborated in an animal study which revealed no significant difference in the size of lesions induced in non-obese diabetic rats and controls (Fouad *et al.* 2002).

The effect of specific acquired immunity on periapical destruction has only been investigated in animal models. Genetically engineered rats with profound defects in both humoural and cellular immunity were less likely to localize infection to the root canal system and developed gross orofacial abscesses and even septic shock (Teles *et al.* 1997). This observation is consistent with the finding that non-immunized animals have an inflammatory infiltrate resembling osteomyelitis extending into the trabecular system of the bone (Dahlén *et al.* 1982); without obvious effect on the size of periapical lesion (Fouad 1997). Very recently, the influence of genetic factors (low-producer of IL6, intermediate- & high-producer of IL1B, low-producer of TNFA) on the development of symptomatic dental abscesses has been suggested (de Sá *et al.* 2007).

In conclusion, both pulpal and periapical disease are inflammatory responses, principally to bacterial infection. In biological terms, they represent a continuum of spread from the tooth crown to the root end. The transition from one to the other is marked by the loss of alveolar bone around the canal exits, radiographically evident as a periapical lesion. Other differences in biological properties arise from the stimulation of epithelial rests of Malassez, causing cysts and the possible difference in response to treatment.

1.3 Historical perspective on concepts underpinning root canal treatment

A reconstruction of the historical development of Endodontology is hampered, as in any discipline by the incomplete threads of information recovered from different parts of the world and belonging to different time periods. The challenge is to piece together the thread fragments by correct time and space location, in order to enable synthesis of a coherent story. This demands access to accurate facts, considerable imagination and intuitive skill, as well as an understanding of the local cultures, life-styles and contemporary demands of those times. Fortunately, these authors had access to prior searches by others in the field, rather than having to rely on their own archaeological, anthropological and scientific searches (Rowe 1968a&b, Francke 1971, Bellizze & Cruse 1980, Cruse & Bellizze 1980a&b, Tsao 1984, Zia & Numberoff 1987).

1.3.1 Concepts of bacterial infection, pulp diagnosis and pulp therapy

Historically, dental treatment was mostly carried out for pain relief (Rowe 1968). As early as 2700 BC, the Chinese had recorded placement of arsenic near the tooth or ear to cure dental pain. Around 500–300 BC, the recommended treatments by Hippocrates, for a painful tooth included cauterisation and "masticatories", application of saffron and cedar gum by Greek physicians (Rowe 1968), or acupuncture by the Chinese (Tsao 1984). The interior of the tooth was suspected as the possible origin of toothache and related to the presence of a nerve supply and inflammation. As a result, a small trephine was used to open the pulp to drain the tooth, and acids or hot wire were used to cauterize the "nerve" during the period of 1600–1800 (Rowe 1968).

The concept of some form of infestation by a worm-like living creature as a cause of dental disease first appeared in China in the Ying Dynasty in 1400 BC (Tsao 1984) and was also later noted in the Mediterranean in 1300 BC (Zia & Numeroff 1987). Antony von Leeuwenhoek was the first known person to identify oral bacteria using an embryonic microscope in 1683; he is widely regarded as the "father of modern microscopy". He considered "worm-infected" cheese to be the source of root canal contamination in 1700 (Ring 1971). It was therefore natural that the formulation of a bacteriological rationale for endodontic treatment would follow; and it came with a bacterio-pathological study of over 200 pulps by Miller based in Berlin in 1891 and published later (Miller 1894a). The concept that antibacterial materials may be used to treat carious dentine started to become established with the use of antiseptics such as oxysulphate of zinc (Miller 1891) and "Pulpol", a zinc oxide/eugenol-based material (Wessler 1894 in Francke 1971). However, the results of pulp treatment (pulp capping) at that time were still unpredictable, with the condition of the dental pulp being diagnosed using an early electric pulp tester (Magitot 1867 in Cruse & Bellizze 1980a) or hot water at various temperatures (Walkhoff 1898 in Cruse & Bellizze 1980a). A further aid to diagnosing occult dental diseases by tapping the suspected teeth to elicit pain was suggested by Hirsch from Germany towards the end of the 18th century (Cruse & Bellizze 1980a).

The progressive development of the biological basis for endodontics is interesting for the adoption of various concepts and the strength of feeling with which debates raged about the merits and validity of different beliefs; even though few writers on either side of the controversy were altogether consistent. Through this process of tension and competition, came the development of both pulp and root canal treatments, as knowledge of the physiology and anatomy of the pulp and tooth as well as the microbial role in the cause of diseases began to take shape.

An example of this type of debate is shown by the issue of the "vitality" of teeth [(Denton & Zachariou 1931)]. Academic thinkers and writers were lined up on opposite sides, as "vitalists" or "non-vitalists". The "vitalists" believed that blood flowed into the pulp through the apical foramen and out through the dentinal wall and periodontal membrane [(Bew 1819 in Denton & Zachariou 1931)]. Thus the whole dentine core of a tooth was considered to "die" immediately after the pulp was destroyed by disease or surgical intervention. The "dead tooth" was then considered to be regarded as a foreign body by the adjacent living tissues leading to inflammation, suppuration and ultimately death of these tissues. Therefore, pulp capping rather than pulp extirpation was preferred and popularized by Koecker (1821). The main opponents to the "vitalistic" theory were eminent scientists studying anatomy and physiology of teeth in England over a time-frame preceding the establishment of the great debate and included Hunter (1771), Cuvier (1814) and Robertson (1835) [(Denton & Zachariou 1931)]. They collectively established the idea that teeth were fastened at the base of the alveolus through their neuro-vascular bundles as well as by the membrane of bone but that neither the blood vessels, nor the nerves from the pulp or the alveolus entered the hard part of the tooth. Thus the practice of pulp extirpation had gained approval.

The debate about the "vitalistic" theory held sway until it was challenged by the new "septic" theory. General surgeons realized the importance of pathogenic organisms in various diseases, leading eventually to aseptic surgical techniques being introduced by Lister (1867). At about this time, the discovery of a parasite called "Leptothrix buccalis" from a tooth surface, in carious lesions and in dentinal tubules by Leber & Rottenstein (1867) from Berlin [(Francke 1971)] lent credence to this notion. The proponents of the "septic" theory therefore suggested the pathogenic organisms as the cause of pulpal disease, loss of tooth vitality, failure of pulp treatments, and suppuration of the pulp leading to alveolar abscesses [(Rogers 1878, Underwood & Milles 1882)]. Therefore successful pulp and root canal treatment were deemed to require the total and absolute destruction of these organisms [(Roger 1878)] using powerful and penetrating antiseptic agents [(Underwood & Milles 1882)].

1.3.2 The origin of root canal treatment

Once it was considered that the dental pulp had been compromised, the idea of removing the dying or dead tissue became established. Pulp extirpation slowly evolved from what was surely considered to be an extremely painful experience involving the use of a hot instrument or corrosive sulphuric or nitric acids to a relatively painless process involving the use of arsenic trioxide prior to extirpation [(Cruse & Bellizze 1980a)]. The use of arsenic trioxide for this purpose was introduced in Europe by Spooner in 1863, although it had already been used by the Chinese since 200 AD for treatment of pulpitis. The potential of leakage of arsenic through the root canal, destroying adjacent vital supporting tissues was recognised even then (Cruse & Bellizze 1980a). Topical cocaine was subsequently adopted for anesthetizing the pulp by Freud in 1884 (Cruse & Bellizze 1980a). The progressive evolution of methods for pulp extirpations and root canal treatments continued through the refinement of the procedures and materials used, by trial and error. The first reference to materials being inserted into a tooth was found in the Ebers Papyrus dated about 1500 BC (Rowe 1968a). The materials were a concoction of fruit of Gebu plant, onion, cake dough, Anest plant and water.

The term “Root canal treatment” did not appear until 1520 AD, when the first reference to any form of canal preparation (‘trephining’) and filling (theriac or other remedies) were made by Benedictus of Faenza (Rowe 1968a). The technical problem of reaching the root apex appeared to be recognised by the fact that intentional root canal treatment and replantation were practised by Bourdet from France in 1757. The importance of reaching the apex following pulp cauterization was also highlighted by John Hunter from London in 1771. These embryonic endodontic procedures were brought to the United States of America by Wooffendale from England in 1783 (Cruse & Bellizze 1980a).

Curiously, the concept of packing the root canal system seemed to take shape earlier than the notion of cleaning the canal system thoroughly. Materials and techniques appear to have been developed from the concepts of packing gold foil into cavities with specifically designed instruments by Hudson in 1809. The use of gutta-percha, chloropercha by Bowman in 1867 and thermoplastized gutta-percha by Clarke in 1865 to compact into the canals appear to have found seed origins around about the same period (Cruse & Bellizze 1980a). Many other root filling materials such as gold wire, oxychloride of zinc cement, wood with carbolic or creosote, cotton with creosote, iodoform or materials containing iodoform or paraform have also been documented (Dental Cosmos 1874). It is interesting to note that within this period, an early form of tooth isolation using rubber dam was introduced by Barnum in 1864. Root canal broaches for pulp extirpation and hoe-like instruments for canal enlargement and shaping were invented in USA by Maynard in 1838 (Cruse & Bellizze 1980a).

In a period following a little later, on the basis of the “septic” theory, Witzel in 1873 applied Lister’s antiseptic technique in pulp and root canal treatment using phenol as the antiseptic agent (Prinz 1917). Other approaches for sterilizing root canals included the use of chlorophenol (Walkhoff 1891 in Cruse & Bellizze 1980b), sodium dioxide (Kirk 1893), a mixture of metallic sodium and potassium (Schreier 1893), 20% to 40% sulphuric acid (Callahan 1894), and electro-medication (Breuer 1890 in Prinz 1917). This latter approach was further popularised and refined by a host of writers, including Rhein (1895 in Prinz 1017), Bethel (1896–97 in Prinz 1917), Zierler & Lehmann (1900 in Prinz 1917), Hoffendahl (1905), Prinz

(1917), Sturridge (1912), Hinman (1921), Johnson (1923) and Appleton (1931). Three percent zinc chloride (Sturridge 1912) or 1% sodium chloride (Prinz 1917) solutions were used as electrolytes. This "sterilization" procedure was subsequently called electro-sterilization (Zierler 1900). The principle agent for electro-sterilization was chlorine which is the active component of sodium hypochlorite solution, the first choice of canal irrigant in the twenty-first century. As the focus on "sterilization" of the root canal grew, so examination of the root canal for bacteria prior to root filling began to be advocated (Onderdonk 1901).

The discovery of X-rays by Roentgen in 1895 had a direct and almost immediate impact on endodontics, as the "blind" procedure found a means of imaging the hidden tissues. They were used for canal length determination during root canal treatment only 3 years later (Kells 1899). Most importantly, the merit of preserving natural teeth either by pulp capping or root filling was becoming established albeit based on basic concepts and principles with scanty biological insight.

1.3.3 The focal infection era

These promising foundations for modern endodontics were shaken when Billings (1904 in Bellizze & Cruse 1980) directed the attention of dentistry and medicine to the apparent relationship between oral sepsis and bacterial endocarditis. The concept was not new, having been raised as early as 700 yrs BC in Assyria, even Hippocrates talked about the link in 40 yrs BC. A more contemporary colleague (WD Miller 1891) had already coined the term "focus of infection" and highlighted a possible link between mouth-germs and systemic disease. It was Rosenow in 1909 (Rosenow 1919), a student of Billings, who presented the "Theory of focal Infection" based on his bacteriologic findings on root canal therapy. He claimed that streptococci were found in many diseased organs and were capable of spreading through the bloodstream to establish other foci of infection at distant sites (Rosenow 1909). Nevertheless, the disastrous consequences of this theory were only truly unleashed, when a lecture delivered to the faculty of McGill University in Montreal, Canada, by an English surgeon, was published in the Lancet (W Hunter 1911). He criticized private dentists ignoring necrosis and sepsis in and around teeth, whilst focusing on creating a "mausoleum of gold over a mass of sepsis to which he saw no parallel in the whole realm of medicine or surgery". He specifically targeted conservative dentists, working in London, who had adopted American methods and skills to build broken dentitions with gold fillings, caps, bridges and dentures. His intention was to encourage dentists to identify poor hygiene and septic foci and correct them through antiseptic dressings and oral health education. Unfortunately, his message was misconstrued and resulted in the dental and medical profession's focus on pulpless teeth as well as other foci, such as tonsils, nasal sinuses, gastro-intestinal tract, appendix, cervix, uterus, ovaries, prostate, and vas deferens.

Extraction of teeth rather than root canal treatment was considered the quickest, easiest and surest means of eliminating oral sepsis. Therefore, the work of the "conservative" dentists perfecting root canal treatment techniques was over-shadowed by the physicians, radiographers and the exodontists.

It was quite remarkable how this clinical practice was driven through sheer force of opinion from the putative senior fraternity of Medicine, which many dentists may have craved to join. The sentiment is clearly expressed by Shandalow (1928), "coincident with the realisation of the intimate interrelationship between medical and dental science, there is soon to be bestowed upon the younger profession, a new dignity, a sort of accolade in the form of elevation to the standard of a medical specialty". The focal infection theory reigned for approximately 50 years upto *circa* 1940. During this era, "evidence" supporting this theory continued to be presented by its major proponents [(Rosenow 1919, Hunter 1921, Price 1923, Shandalow 1928 and many others)]. Fears of fatal oral sepsis from deficient root canal treatments led to widespread extraction of pulpless teeth and the disappearance of endodontic treatment. Endodontics had virtually disappeared from many dental schools, except for the teaching of pulp biology. In some areas treatment was restricted to anterior teeth as it was believed too difficult to eradicate the infection from posterior teeth. Dentists who advocated extraction of all teeth were known as the "one hundred percenters" [(Kirt & Antony 1930)]. Interestingly, the "focal infection theory" did not influence the practice of dentistry in continental Europe.

The leading opponents of the focal infection theory [(Johnson 1926, Miller 1926)] challenged the validity of supporting evidence for the theory, on the grounds of poor study design, lack of controls and confounding factors. Johnson (1926) therefore advocated retention of pulpless teeth whenever they were amenable to successful treatment and encouraged dentists to take a more rational approach to making decisions about the management of pulpless teeth. Fortunately, these opponents together with a group of conscientious and skilful root canal therapists promoted good quality root canal treatment and followed the principles used today [(Callahan 1911, Prinz 1917, Hinman 1921, Blayney 1922, Johnston 1923, Crane 1926, Grove 1926, Peterbaugh 1926, Rhein 1926, Coolidge 1927, Appleton 1931, Buchbinder 1936, Auerbach 1938)]. They adopted diagnostic radiography, aseptic technique, as well as bacteriological and histological methods to assess their treatment. Some of them analysed the clinical outcome of their treatment systematically and reported favourable success rates. Rhein (1912) advocated the use of rubber dam, good access to canals, cleansers and filling with Schreier's paste (kaliumnatrium) to dissolve organic tissue and chloropercha to fill the root canal system. He also emphasised the importance of the coronal seal. Thus this group of highly skilled and visionary clinicians acted as custodians for the discipline of Endodontics. Gradually, the pendulum swung back to conservation of teeth, so that by the 1950's, endodontic treatment was accepted by the medical profession and the endodontic specialty was given approval.

1.3.4 The basis for modern endodontics

The principles of contemporary pulp and root canal treatment had been fully established and those presented by Hall (1928) are still deemed to hold true in the 21st century. He suggested that endodontic treatment should: never destroy a vital pulp; use surgical asepsis; use measurement to control instrument trauma; not be performed without radiographs; not enlarge apical foramen or go beyond the cemento-dentinal junction; not pump, push, or expel septic matter through the apical foramen; not use tissue-destroying drugs in root canals; never leave a tooth unsealed; not be based on a few special cases; and never be observed for only a short time.

Recognition of the role of bacteria in the pathogenesis of periapical disease was interrupted by many digressions and problems, both scientific and political. The importance of this heritage is that the “cultural” attitudes amongst members of this discipline have shaped modern endodontics. Fashions continue to dominate the cycles of change that have seen either biomechanical or biological aspects alternate in apparent importance. Overall though dentists identify more closely with biomechanical reasoning and therefore the biological rationale has been neglected to a greater extent (Noyes 1922, Naidorf 1972).

Since the introduction of X-rays in dentistry, the use of radiographs has become an integral procedure for diagnosing apical periodontitis, facilitating root canal treatment and assessing treatment outcome. The evidence for the basis of its use in diagnosing apical periodontitis is reviewed below.

1.4 Radiographic methods for assessment of periradicular diseases

1.4.1 Correlation between histological and radiographic findings

Radiographs were used for diagnosing dental diseases soon after their invention in 1895. Although the gold standard for assessing the health of the periapical tissues is histological examination, the approach cannot ethically be applied in routine practice. Thus various non-invasive tissue imaging methods have been explored for their utilities in diagnosis, conditional upon absence of harmful side effects or balanced against such effects. Radiographic imaging has been a well accepted surrogate measure for the histological condition of the periapex on the basis of a positive correlation between histological and radiographic findings (Brynolf 1967). Dual analysis of 318 maxillary incisors in human cadavers found strong agreement (93%) between the two examinations. There was 98% agreement for cases without inflammation and 81% – 88% agreement for cases with apical inflammation (Brynolf 1967). Thirty years later, Green *et al*. (1997) carried out a similar study but without limiting the type and position of teeth investigated. The sample size was smaller (29 root filled teeth and 10 healthy untreated teeth as control) but they found 100% correlation between histological and radiographic examination of the periapical tissue for healthy untreated teeth (n = 10) and for teeth with periapical radiolucent lesions (n = 10). However, inflammation was present in the periapical tissue in 26% (n=5) of the teeth without a periapical radiolucent lesion (n=19). It was therefore concluded that the specificity was 100% but the sensitivity was about 66% (10/15) for radiographic detection of periapical disease. This low sensitivity compared with that reported by Brynolf (1967) may be attributed to the bone structure overlying posterior teeth. Surprisingly, the respective figures for histological and radiographic examination of 53 block sections of root-filled teeth from cadavers, reported by Barthel *et al*. (2004) were much lower: 73% for specificity and 35% for sensitivity. The difference in findings between Green *et al*. (1997) and Barthel *et al*. (2004) may be attributable to the difference in the protocols for histological sectioning and radiographic technique. The former carried out serial sectioning whilst the latter only examined every 10th histological section, possibly resulting in a higher chance of false negative findings. Details of the radiographic technique in the former study (Green *et al*. 1997) were scant and so a comparison could not be made.

Factors affecting sensitivity were all related to the relative mineral tissue loss; including the extent of the lesion (Bender & Seltzer 1961); inflammation (Pitt Ford 1984); thickness of the overlying cortical bone (Shoha *et al*. 1974); and superimposition of the lesion by other anatomical structures. The latter problem may be reduced by taking more than one radiograph at different horizontal angles (Tidmarsh 1987). Recently, cone-beam volumetric tomography which is a relatively new three-dimensional imaging technique requiring only 8% of the effective dose of a conventional computed tomography scanner (Mah *et al*. 2003), is able to overcome the problem of superimposition. It has rapidly gained popularity amongst Endodontists (Cotton *et al*. 2007, Patel *et al*. 2007, Estrela *et al*. 2008) despite an absence of tests for sensitivity or specificity. It has been determined that 34% of lesions associated with posterior teeth failing to be detected by conventional periapical radiograph, could be detected by cone beam tomography (Low *et al*. 2008). Its routine use is however, not recommended due to higher radiation (x 2-3) (Arai *et al*. 2001).

1.4.2 Alternative imaging of periapical tissue

Considering the side effects of X-radiation, alternative imaging techniques such as echographic (Cotti *et al*. 2002) and magnetic resonance (Gahleitner *et al*. 1999, Tutton & Goddard 2002) imaging have been tested for detecting and diagnosing periapical lesions. These techniques have been used to examine soft tissues rather than bony structures (Cotti & Campisis 2004). Although both techniques showed promising potential in assessing periapical lesions, ultrasound real-time imaging could not consistently identify the tooth associated with the lesion (Cotti *et al*. 2002) and magnetic resonance imaging was compromised by artifacts due to metallic restorations (Tutton & Goddard 2002).

1.4.3 Interpretation of radiographic images

In view of the problems of interpretation of two-dimensional radiographs, errors in diagnosing periapical lesions are inevitable. Inconsistency in interpretation by different observer groups is well recognized [(Reit & Hollender 1983, Lambrianidis 1985)]. The agreement in repeated reading of radiographs by the same observer (intra-observer agreement) ranged between 53% and 89% [(Goldman *et al.* 1974, Zakariasen *et al.* 1984)]. The employment of at least two observers [(Halse & Molven 1986)] reduced the potential systematic error caused by a single observer, the inter-observer variation however increased with number of observers [(Lambrianidis 1985)] and variation in expertise [(Reit & Hollender 1983)]. Reported inter-observer agreements amongst six observers ranged from 39% to 47% [(Goldman *et al.* 1974, Reit & Hollender 1983)]. Agreement amongst nine observers was 38% [(Lambrianidis 1985)] and reduced to 2–8% amongst twelve examiners [(Abdel Wahab *et al.* 1984)]. Consistent diagnosis of widened periodontal ligament space was more difficult to achieve than that of well developed periapical lesions [(Reit & Hollender 1983)].

Different strategies have therefore been derived to reduce errors and variations in interpretation. Visualization of the radiolucent lesion could be enhanced by ensuring optimal viewing conditions: blocking of extraneous light [(Welander *et al.* 1983)], using magnification [(Brynolf 1979)], and avoiding tiredness due to long duration of viewing [(Goldman *et al.* 1972)]. In order to reduce the potential bias related to individual observer's experience and emotional influence [(Goldman *et al.* 1972)], treatment providers should be excluded as radiographic observers when assessing treatment outcome [(Goldman *et al.* 1972)]. Training or pre-calibrating radiographic observers using a standard set of radiographs and periapical scoring systems [(Eckerbom *et al.* 1986)] could improve intra- and inter-observer agreement.

Two indices have been used to standardize observer's interpretation of periapical status in epidemiological studies, they have also been used to assess outcome of treatment. The first index, the "probability index" (RPI) (Table 1.4.1 – Overleaf) was introduced by Reit & Gröndahl (1983). It has been adopted by studies on decision-making for re-treatment options [(Reit 1986, Kvist 2001, McCaul *et al.* 2001)] but is rarely used in clinical outcome studies [(Peters & Wesselink 2002, Stoll *et al.* 2005)]. The "periapical index" (PAI) (Table 1.4.1) was subsequently developed by Ørstavik *et al.* (1986) using the radiographic material from Brynolf's study (1967) for observer calibration (Figure 1.4.1). As already iterated, the study was limited to maxillary incisors, therefore, the validity of applying PAI on other tooth types is questionable. Nevertheless, the inter- & intra-observer agreement improved after calibration using this system [(Ørstavik *et al.* 1986)] and the agreement remained satisfactory when the same set of radiographs was re-examined several years later [(Molven *et al.* 2002)].

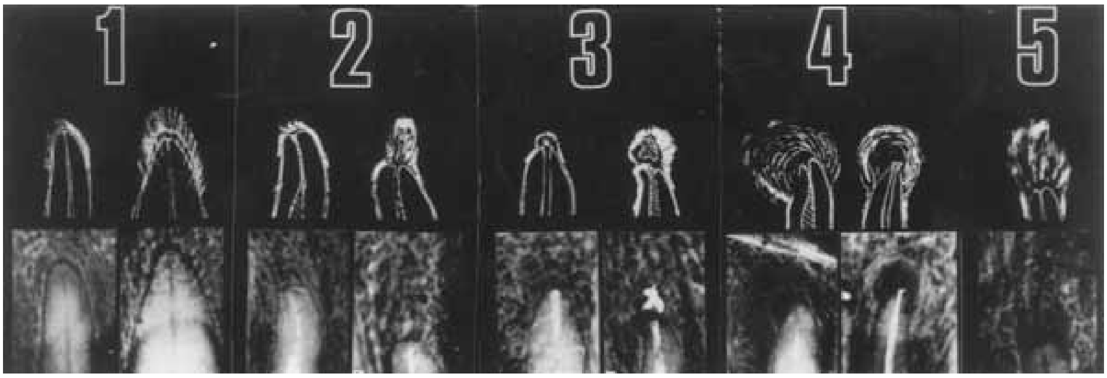
Table 1.4.1 The probability index (PRI) (Reit & Gröndahl 1983) and periapical index (PAI) (Ørstavik *et al*. 1986)

PRI		PAI						
			Histological groups and finding in periapical tissues (Brynolf 1967)					
score	**criteria**	**Score**	**Histological groups**		**Presence of inflammatory cells in apical soft tissues**	**Type of periapical marrow**	**Shape and width of apical tissue**
1	Periapical destruction of bone almost definitely not present	1	N	Normal group,	None	Fat or fat & fibrous marrow	No increase in width
			M	Marginal group	No or very few scattered inflammatory cells	Fat or fat & fibrous marrow	Increase in width apically (an laterally) with “tapering-widening”
2	Periapical destruction of bone probably not present	2	I	Mild, chronic inflammation	Very few or few round cells	Fat or fat & fibrous marrow	Slight increase of width in and at foramen
			I*	Mild, chronic, more active inflammation	Very few or few round cells	Fibrous reaction in periapical marrow	Slightly larger, more irregular, increased width at foramen
3	Unsure	3	II	Moderate, chronic inflammation	Moderate to relatively large amount of round cells, no granulocytes	Fat or fat & fibrous marrow	Marked increase of width
4	Periapical destruction of bone probably present	4	III	Severe, chronic inflammation	Abundant plasma cells and/or lymphocytes, possibly few granulocytes	Fat & fibrous marrow	Marked or pronounced increase of width
5	Periapical destruction of bone almost definitely present	5	IV	Severe, chronic inflammation with features of exacerbation	Abundant plasma cells and/or lymphocytes, abundant or fairly abundant granulocytes	Fat & fibrous marrow, or Fibrous marrow	Marked or pronounced increase of width

Instruction for application of PAI

- Find the reference radiograph where the periapical area most closely resembles the periapical area you are studying. Assign the corresponding score to the observer root.
- When in doubt, assign higher score,
- For multi-rooted teeth, use the highest of the scores given to the individual roots.
- All teeth must be given a score.

Figure 1.4.1 Reference set of radiographs with corresponding line drawing and their associated PAI scores (adopted from Ørstavik *et al*. 1986)



The PAI has been used by many research groups for epidemiological surveys (Eriksen *et al*. 1988, 1995, Eriksen & Bjertness 1991, Sidaravicius *et al*. 1999, Kirkevang *et al*. 2000, 2001a, Boucher *et al*. 2002, Jimenez-Pinzon *et al*. 2004, Segura-Egea *et al*. 2004, Segura-Egea *et al*. 2008, Touré *et al*. 2008) as well as for clinical outcome studies (Ørstavik *et al*. 1987, Trope *et al*. 1999, Delano *et al*. 2001, Friedman *et al*. 2003, Huumonen *et al*. 2003, Farzaneh *et al*. 2004a, Doyle *et al*. 2007, Penesis *et al*. 2008). Some issues related to the application of this index for assessing outcome of treatment will be discussed in a later section (Section 1.9.1.2). The inter-observer agreement was improved by pre-calibration using the above indices, but remained imperfect. Joint evaluation to obtain consensus for those cases on which two observers disagreed was therefore recommended (Halse & Molven 1986).

1.5 Biological rationale of root canal treatment

The contemporary biological rationale for root canal treatment was developed from historical groundwork (Hall 1928) and evidence from clinical microbiological studies.

1.5.1 Microbiology of untreated teeth with apical periodontitis

1.5.1.1 Type of root canal flora

The polymicrobial nature of root canal infection has been well established since the landmark clinical microbiological study by Sundqvist (1976). The quantity of bacteria per sample obtained from previously untreated teeth ranged from 10^1 (Hoshino *et al*. 1992) to 10^8 (Sjögren *et al*. 1991) colony forming units. The number of bacterial strains ranged from 1 – 12 per tooth (Bergenholtz 1974, Wittgow & Sabiston 1975, Sundqvist 1976, Byström & Sundqvist 1985, Gomes *et al*. 1996a, Lana *et al*. 2001) and was positively correlated with the size of periapical bone destruction and presence of pain (Sundqvist 1976).

Early investigations revealed that the root canal bacteria corresponded to the oral flora and were dominated by the *Streptococcus* species (Brown & Rudolph 1957, Winkler & Van Amerogen 1959, Engström & Frostrel 1961, Kantz & Henry 1973). With advances in anaerobic culture techniques, the infection was found to be dominated by anaerobic bacteria (Bergenholtz 1974, Sundqvist 1976, Hirai *et al*. 1991, Gomes 1994, Gomes *et al*. 1996a, Gomes *et al*. 2004, Chu *et al*. 2005), consistent with the findings using contemporary molecular culture-independent techniques (Rolph *et al*. 2001, Munson *et al*. 2002, Vianna *et al*. 2005, Sassone *et al*. 2008a&b). Reports on the relative proportion of Gram-negative or Gram-positive anaerobic bacteria have been inconsistent. In a classical study of 32 traumatized teeth with pulpal necrosis and intact crowns, the root canal infection associated with periapical lesions was dominated by Gram-negative anaerobic bacteria (Sundqvist 1976), consistent with Bergenholtz (1974) and Wittgow & Sabiston (1975). In contrast, gram-positive anaerobes dominated in non-vital teeth with carious lesions (Ando & Hoshino 1990, Hirai *et al*. 1991, Hahn *et al*. 1991).

The association of bacterial species with specific clinical conditions have been investigated in a number of studies. The conditions investigated have included, symptoms (Sundqvist 1976, Yoshida *et al*. 1987, Hashioka *et al*. 1992, Gomes *et al*. 1994, Gomes *et al*. 1996a, Siqueira *et al*. 2004, Sassone *et al*. 2008b), swelling (Gomes *et al*. 2004), sinus (Gomes *et al*. 2004, Sassone *et al*. 2008b), periodontal disease (Kipiotic *et al*. 1984, Kobayashi *et al*. 1990), and exudation from root canals (Sundqvist 1976, Baumgartner *et al*. 1999, Gomes *et al*. 2004). Bacterial species implicated in swelling and symptoms were dominated by Gram-negative anaerobes: *Prevotella intermedia/nigrescens* (Sundqvist 1976, Yoshida *et al*. 1987, Gomes *et al*. 1994, Gomes *et al*. 1996a, Gomes *et al*. 2004), *Porphyromonas* spp. (Hashioka *et al*. 1992, Gomes *et al*. 2004), and *Fusobacterium* spp. (Gomes *et al*. 2004). Others species included, *Peptostreptococcus* spp. (Sundqvist 1976, Yoshida *et al*. 1987, Hashioka *et al*. 1992, Gomes *et al*. 2004), Eubacteria (Sundqvist 1976, Hashioka *et al*. 1992) and *Campylobacter sputorum* (Sundqvist 1976). Using checkerboard DNA-DNA hybridization for bacterial identification, a high level of *Fusobacterium*, *Veillonella*, *Treponema*, *Enterococcus*, and *Campylobacter* species have been found in symptomatic teeth (Sassone *et al*. 2008a).

Despite the putative associations, a definitive cause/effect relationship remains elusive, presumably because the problems are strain-dependent (Gulabivala 2004a).

1.5.1.2 Spatial distribution of root canal flora

Light (Shovelton 1964) and scanning electron microscopy (Sen *et al.* 1995) have revealed the presence of bacteria in all areas of the root canal system in infected teeth, with a greater number in the coronal compared to the apical portion of the root canal system (Shovelton 1964). There was a polar distribution of bacteria in oval canals and bacterial penetration of up to half the thickness of dentine especially in cases of chronic, as opposed to acute infection (Shovelton 1964). This presence of bacteria at varying distances in the deeper layers of dentine has also been described in studies using culture-dependent techniques (Chirnside 1961, Ando & Hoshino 1990, Sen *et al.* 1995, Peters *et al.* 2001).

Examining the apices of carious teeth with attached lesions using light and transmission electron microscopy, bacteria were predominantly found to be suspended in the moist root canal lumen or attached to the dentine walls (Nair 1987). The presence of a neutrophil barrier or an epithelial plug was thought to prevent the egress of bacteria from the root canal into the chronic lesion (Nair 1987). Only in acute exacerbation did the bacterial front extend into the lesion (Nair 1987). The existence of an amorphous plaque-like material on the dentinal walls described by Shovelton (1964), Nair (1987) and

Molven *et al.* (1991) may have been the earliest descriptions of the "biofilm" present on root canal surface. A recent scanning electron microscopic study on 27 teeth with carious and radiolucent lesions revealed bacterial cells as aggregates of rods observed close to the apical foramen within the root canal (Siqueira & Lopes 2001). In one of the teeth examined, bacterial aggregate with different morphotypes extended beyond the apical foramen but the associated condition of this tooth was not reported.

1.5.1.3 Bacterial invasion of periapical tissue

The existence of extra-radicular infection in asymptomatic cases remains the subject of debate with no definitive conclusion. This issue has significant implications in the outcome of non-surgical root canal treatment as these bacteria are inaccessible to the treatment. However, none of the previous studies has investigated extra-radicular infection in previously untreated cases. The only common consensus on this issue was that amongst the root canal bacteria, *Actinomyces* spp. were recognized to be able to establish extra-radicularly and perpetuate the inflammation at the periapex without causing acute symptoms (Nair 2006). This is supported by a number of reports of individual refractory cases (Sundqvist & Reuterving 1980, Ramachandran Nair & Schroeder 1984, Happonen 1986, Nishimura 1986, Byström *et al*. 1987, Sjögren *et al*. 1988, Nair *et al*. 1999, Hirshberg *et al*. 2003). Although yeasts such as *Candida albicans* also possessed abilities to invade and survive in the apical tissue, a study using culture-independent technique could not detect its presence in any of the 103 surgically removed periapical granulomas (Waltimo *et al.* 2003). The opponents of the existence of extra-radicular infection believe that a "solid granuloma" does not harbour infectious agents within the inflamed periapical tissue, but that micro-organisms are consistently present in the periapical tissue of cases with clinical signs of acute exacerbation, abscesses and draining sinus (Nair 1987). Various bacterial species other than *Actinomyces* spp. have been recovered from the persistent periapical lesions of root-filled teeth by many workers (Grossman 1959, Tronstad *et al*. 1987, 1990, Iwu *et al*. 1990, Wayman *et al*. 1992, Kiryu *et al*. *et al*. 1994, Abou-Rass & Bogen 1998, Sunde *et al*. 2002, Sunde *et al*. 2003). In these studies, bacterial samples were either collected directly from the lesion during endodontic surgery (Grossman 1959, Iwu *et al*. 1990) or from the cementum of amputated roots or the attached soft tissue lesions (Tronstad 1990, Kiryu *et al*. 1994, Abou-Rass & Bogen 1998, Sunde *et al*. 2002). Contamination by the oral and intra-radicular bacteria during bacterial sampling was therefore inevitable despite stringent decontamination protocols (Sunde *et al*. 2002). After reviewing previous evidence, Nair (2006) concluded that extra-radicular infections only occur in teeth with: (1) exacerbating apical periodontitis lesion, (2) periapical actinomycosis, (3) pieces of infected root dentine (displaced into the periapex during root canal instrumentation or having been cut off from the rest of the root by massive apical resorption), or (4) infected periapical cyst, particularly in periapical pocket cysts with cavities open to the root canal.

1.5.2 Effect of root canal treatment procedures on bacterial flora

Monitoring of changes in bacterial load and relative proportion of bacterial species following each stage of the root canal treatment has been a valuable method for testing the efficacy of such procedures. Both reduction in bacterial cell numbers and the proportion of teeth with negative cultures have been used as outcome measures.

The most influential biological evidence for contemporary root canal treatment was provided by a series of studies from Sundqvist and colleagues (Byström & Sundqvist 1981, 1983, 1985, Byström *et al.* 1985, Sjögren & Sundqvist 1987, Sjögren *et al.* 1991). They evaluated the effect of various root canal treatment procedures on the bacterial flora, both qualitatively and quantitatively, using standardized methodology. The antibacterial effect of mechanical preparation was improved by sodium hypochlorite irrigation (0.5%, 5.0%), and further by alternate irrigation with ethylene-diamine-tetra-acetic acid (EDTA) and 5.0% sodium hypochlorite solution. The addition of ultrasonic activation exacted additional improvement as did calcium hydroxide dressing. The irrigation regimes reduced the number of bacteria from an initial range of 10^2–10^8 cells to 10^2–10^3 cells after initial debridement, which reduced further to no recoverable cells after inter-appointment dressing with calcium hydroxide.

When “negative culture” was used as the outcome measure, it was achieved after using water or saline irrigation in 4.6% – 75% of cases (Ingle & Zeldow 1958, Nicholls 1962, Grahnén & Krasse 1963, Zeldow & Ingle 1963, Byström & Sundqvist 1981, Ørstavik *et al.* 1991, Dalton *et al*. 1998). The frequency of negative culture (25% – 98%) increased substantially when sodium hypochlorite (concentration of 0.5% – 5.0%) was used as the irrigant during mechanical preparation (Cvek *et al.* 1976a, Byström & Sundqvist 1981, 1983, 1985, Sjögren & Sundqvist 1987, Yared & Bou Dagher 1994, Gomes *et al.* 1996, Shuping *et al*. 2000, Peters *et al*. 2002, Kvist *et al*. 2004, Vianna *et al*. 2006, Siqueira *et al*. 2007a, Siqueira *et al*. 2007b, Siqueira *et al*. 2007c). This was also corroborated by the results of a culture-independent microbiological study (Sakamoto *et al*. 2008). The wide range of results may be attributable to the variation in pre-operative condition of the teeth, concentration and volume of sodium hypochlorite solution, the size of the canal preparation and the microbiological methods. Those teeth with high bacterial counts pre-operatively were more likely to have positive culture after debridement (Byström & Sundqvist 1981). No significant difference was however found between those teeth debrided with 0.5% or 5% sodium hypochlorite solutions (Byström & Sundqvist 1983). The findings on the influence of the size of apical preparation on bacterial load reduction have been inconsistent. Some groups have shown more effective bacterial debridement with larger compared to smaller apical preparation sizes (Parris *et al.* 1994, Rollison *et al.* 2002, Card *et al.* 2002), whereas others failed to show such a difference (Yared & Bou Dagher 1994, Coldero *et al.* 2002, Wang *et al*. 2007). The discrepancy may again be attributed to the variation in clinical condition of the samples and microbiological method used.

The additional use of ultrasonic agitation of the sodium hypochlorite irrigant (Sjögren & Sundqvist 1987, Carver *et al.* 2007) and alternate irrigation with EDTA and sodium hypochlorite (Byström & Sundqvist 1985) during mechanical preparation achieved an even higher frequency of negative culture. The use of chlorhexidine gluconate (concentration of 0.12% – 2.5%) solution or 2% chlorhexidine gel for irrigation was suggested ten years ago (Kuruvilla & Kamath 1998) and began to gain acceptance. However, the number of negative cultures achieved using chlorhexidine irrigation was similar to (Waltimo *et al.* 2005, Siqueira *et al.* 2007c) or lower than (Vianna *et al.* 2006) using sodium hypochlorite irrigation; corroborated by a study on previously treated teeth (Schirrmeister *et al.* 2007). Biosept® (a quaternary ammonium compound) was used for irrigation in the 1960s and gave 32% (Grahnén & Krasse 1963) and 40% (Engström 1964) negative cultures, respectively.

In cases treated over multiple visits, culture reversals were observed during the inter-appointment period, if an active antibacterial dressing was not used between appointments (Byström & Sundqvist 1981). The reversals were attributed to re-growth of residual bacteria or bacterial recontamination due to coronal leakage (Ingle & Zeldow 1958, Stewart *et al.* 1961, Myers *et al.* 1969, Bence *et al.* 1973, Tsatsas *et al.* 1974). The benefit of inter-appointment dressing of the root canal system with calcium hydroxide has been documented following mechanical preparation using water irrigation (Ørstavik *et al.* 1991, Yared & Bou Dahger 1994), sodium hypochlorite irrigation (Byström *et al.* 1985, Reit & Dahlén 1988, Sjögren *et al.* 1991, Yared & Bou Dagher 1994, Shuping *et al.* 2000, Kvist *et al.* 2004) or sodium hypochlorite irrigation with a "final" EDTA rinse (McGurkin-Smith *et al.* 2005). In contrast, some studies (Peters *et al.* 2002, Waltimo *et al.* 2005, Siqueira *et al.* 2007a, Wang *et al.* 2007) found no significant benefit of dressing with calcium hydroxide between treatment visits. Other antibacterial dressing agents tested included: Nebacin (neomycin-bacitracin) antibiotic giving 60% negative cultures (Grahnen & Krasse 1963); Cresatin (m-cresyl acetate)/Camphorated paramonochlorophenol (CMCP)/polyantibiotic paste giving 76% negative cultures (Tsatsas *et al.* 1974); CMCP or camphorated phenol giving 67% negative culture (Byström *et al.* 1985); clindamycin antibiotic giving 76% negative culture (Molander *et al.* 1990); Septomixine antibiotic (framycetin sulfate) giving 83% negative culture (Tang *et al.* 2004), $Ca(OH)_2$/CMCP/glycerin paste giving 91% negative culture (Siqueira *et al.* 2007b), and $Ca(OH)_2$/chlorhexidine gel giving 91% negative culture (Wang *et al.* 2007).

Although the composition of the recovered root canal micro-flora varied during treatment, there was no indication that specific bacteria were implicated in persistent infections after chemo-mechanical debridement of previously untreated root canals (Byström & Sundqvist 1981, 1983, 1985, Olgart 1969, Cvek *et al.* 1976a, Gomes *et al.* 1996b).

Certain bacterial species are more prevalent in positive cultures and included facultative gram-positive bacteria (*Actinomyces* species, *Enterococcus species*, *Lactobacillus* species, *Propionibacterium* species, *Streptococcus* species, *Staphylococcus* species) and Yeasts (Bender & Seltzer 1950, 1952, Winkler & van Amerongen 1959, Crawford & Shankle 1961, Melville & Slack 1961, Engström 1964, Goldman & Pearson 1969, Myers *et al.* 1969, Tsatsas *et al.* 1974, Cvek *et al.*

1976a, Sjögren & Sundqvist 1987, Reit & Dahlén 1988, Molander *et al.* 1990, Sjögren *et al.* 1991, Reit *et al.* 1999, Peters *et al.* 2002, Chavez de Paz *et al*. 2003, Sakamoto *et al*. 2007, Siqueira *et al*. 2007c).

The efficacy of the conventional sampling technique to predictably recover the residual apical bacteria has been challenged (Goria *et al.* 2003). Their speculation was supported by the findings from a microscopic study which revealed presence of residual bacteria in 14 out of 16 amputated mesial roots of molar teeth immediately following one-visit treatment using stringent canal decontamination protocol with sodium hypochlorite and EDTA as the canal irrigants (Nair *et al.* 2005). The fate of these persistent bacteria following obturation of the canal system and provision of coronal restoration has not been followed.

1.5.3 Microbiology of root treated teeth with persistent apical periodontitis

The microbial and non-microbial causes of primary root canal treatment failure have been thoroughly reviewed by Nair (2006). Histo-pathological studies suggested that the most likely cause of treatment failure was intra-radicular bacteria residing in accessory canals or alongside the root-filling (Andreasen & Rud 1972, Lin *et al*. 1991, Nair 1987, Nair *et al*. 1990a, Lin *et al.* 2008). In some instances, failure has been caused by: extra-radicular actinomycosis (Sundqvist & Reuterving 1980, Nair & Schroeder 1984, Happonen 1986, Nishimura 1986, Byström *et al*. 1987, Sjögren *et al*. 1988, Nair *et al*. 1999); cystic apical periodontitis (Nair 1993); foreign body reaction to cholesterol crystals (Nair 1993), extruded dentine chips (Byström *et al*. 1987), extruded calcium hydroxide (Koppang *et al*. 1992), extruded sealer (Koppang *et al*. 1992), extruded gutta-percha filling material (Nair 1990b), extruded amalgam (Koppang *et al*. 1992), or extruded cellulose components from paper points, cotton wool, or pulses (Simon *et al*. 1982, Koppang *et al*. 1989).

The intra-radicular bacteria could either be those surviving treatment protocols (Byström & Sundqvist 1981, 1983, 1985, Cavalleri *et al*. 1989, Gomes *et al*. 1996b, Chavez de Paz *et al*. 2003) or those introduced during or after treatment, for instance because of coronal leakage (Engström 1964, Myers *et al*. 1969, Siren *et al*. 1997, Waltimo *et al*. 1997). Many studies have evaluated the intra-radicular micro-flora associated with failed root canal treatment (Siren *et al*. 1997, Waltimo *et al*. 1997, Sundqvist *et al*. 1998, Molander *et al*. 1998, Peciuliene *et al*. 2000, 2001, Hancock *et al*. 2001, Cheung & Ho 2001, Rolph *et al*. 2001, Egan *et al*. 2002, Pinheiro *et al*. 2003, Rõças *et al*. 2004a, Adib *et al*. 2004, Gomes *et al*. 2008). They have collectively found that when the technical quality of root canal treatment was satisfactory, not only was the diversity of residual species reduced but they were dominated by Gram-positive facultative organisms, in contrast to the flora in previously untreated teeth with periapical disease (Sundqvist 1976). Similarly, a significant association was also found between poor coronal restorations and the recovery of Gram-positive facultative *Streptococcus* spp. and yeasts (Pinheiro *et al*. 2003). The above associations could not be found in a later study by the same group (Gomes *et al.* 2008) using molecular techniques for bacterial detection and identification. However, the majority of the teeth with technically good root fillings had no or poor quality coronal restorations in the latter study. The interactive influence of quality of root filling and coronal restoration on type of bacterial species implicated in failed treatment does not appear to have been systematically explored.

The most frequently detected species using either culture-dependent or culture-independent method has been *Enterococcus faecalis* [Molander *et al.* 1998, Sundqvist *et al.* 1998, Hancock *et al.* 2001, Peciuliene *et al.* 2001, Pinheiro *et al.* 2003, Rôças *et al.* 2004a, Gomes *et al.* 2008], although some studies have failed to detect it [Gomes *et al.* 1996b, Cheung & Ho 2001, Rolph *et al.* 2001]. The significant association of this species with root treated teeth and persistent periapical disease was also revealed by a culture-independent study [Rôças *et al.* 2004b]. A different perspective was provided by another culture-independent study of teeth with variable periapical status requiring retreatment one year after initial therapy [Kaufman *et al.* 2005]. They found the periapical status of the teeth was significantly associated with the presence of bacterial DNA but was not associated with the presence of *E. faecalis* DNA. Other frequently occurring species include *Propionibacterium* species, *Streptococcus* species, *Lactobacillus* species and Yeasts [Waltimo *et al.* 1997, Sundqvist *et al.* 1998, Molander *et al.* 1998, Peciuliene *et al.* 2001, Hancock *et al.* 2001, Cheung & Ho 2001, Egan *et al.* 2002, Rôças *et al.* 2004a, Adib *et al.* 2004].

The variation in the microbiological findings of previously treated teeth may be attributable to the method for retrieval of samples from root canal systems obturated with root-filling material [Molander *et al.* 1998], the quality of previous root canal treatment [Cheung & Ho 2001] and presence of subtle signs of coronal leakage [Adib *et al.* 2004]. Use of either mechanical instruments or organic solvents (chloroform, xylene, halothane) to remove the root-filling material may potentially kill remaining bacteria by generation of frictional heat or direct contact with the solvent [Molander *et al.* 1998]. Sampling from extracted teeth *in vitro* does not pose the same problems of root-filling-material removal [Fukushima *et al.* 1990, Adib *et al.* 2004]. These studies recovered a wider spectrum of bacteria with mixed cultures in 52% [Fukushima *et al.* 1990] to 100% [Adib *et al.* 2004] and single culture infections in 10% of cases [Fukushima *et al.* 1990]. However, the results of the latter study might also be influenced by the unsatisfactory technical quality of previous treatment in all the teeth examined. Cheung & Ho (2001) noted that teeth with acceptable coronal restorations and technically unsatisfactory root-fillings contained a broader range of bacterial species. A trend of single culture infections has also been evident in other studies; Siren *et al*. (1997) found that a third of *Enterococcus faecalis* cases were in pure culture, Waltimo *et al*. (1997) found 13% of yeasts in pure culture, Sundqvist *et al*. (1998) found single species infections in 19 cases, Molander *et al*. (1998) found only 1-2 strains in 85% of the teeth and Peciuliene *et al*. (2000) often found *Enterococcus faecalis* in pure culture. The different profiles of bacteria in previously untreated and treated teeth with apical periodontitis may potentially influence the outcome of primary and secondary root canal treatments and warrant different canal disinfection strategies.

1.6 Guidelines and standards for root canal treatment

Whilst the Endodontic literature is replete with evidence of earnest work of many investigators into the problem of management of root canal infection and periapical disease, there is no optimal standardized protocol for root canal treatment. Clinicians are left to decide on their own approach from the wealth of published information. The demand for standardization of the root canal treatment procedure was raised at the beginning of the last century [Crane 1917, Milton 1918]. On the basis of biological evidence, contemporary quality guidelines for root canal treatment are provided by societies of Endodontology in UK [British Endodontic Society 1983], Europe [European Society of Endodontology 1994, 2006] and Canada [Canadian academy of Endodontics 2006]. They have collectively highlighted the importance of a number of steps: (1) use rubber dam for tooth isolation to facilitate the practice of aseptic technique; (2) prepare the canal as close as possible to the apical constriction located between 0.5 and 2 mm from the radiographic apex [European Society of Endodontology 2006] or the cemento-dentinal junction [Canadian academy of Endodontics 2006]; (3) taper the preparation from the crown to the apex; (4) irrigate the canal using solution with disinfectant and organic debris dissolving properties; (5) dress the canal with disinfectant between visits; (6) fill the canal with appropriate biologically acceptable material only when the infection is considered to have been eliminated and the canal can be dried; (7) extend the canal filling to the full working length with no space between canal filling and canal wall; in addition no canal space should be visible beyond the end-point of the root canal filling; and (8) prevent bacterial recontamination of the root canal system or fracture of the tooth with an adequate restoration. All three societies have recommended clinical and radiographic assessment of treatment outcome for quality assurance purposes.

1.7 Variation in teaching and practice of root canal treatment

The teaching of Endodontics in undergraduate curricula was traditionally provided by teachers within the Department of Conservative Dentistry in the UK [Shovelton 1979]. In other countries, Endodontics was taught in a separate department, examples included Universities of Maryland, Southern California, Stockholm [Kidd 1979] and Universities of Lisbon and Oporto in Spain [De Almeida 1984]. Although the amount of time dedicated to the laboratory teaching varied enormously from school to school, there was a remarkable degree of agreement on specific points of Endodontic technique taught nationally and internationally [Kidd 1979].

In general, undergraduate endodontic curricula competed unfavorably with other dental disciplines and a need to devote more time to endodontics at undergraduate level has repeatedly been acknowledged [Kidd 1979, De Almeida 1984, Dummer 1991]. The insufficient dedication of time to teaching endodontics has resulted in a considerable gap of knowledge and practical expertise to bridge, in order to meet the demands of practice by graduating dentists in the UK (Brookman 1991, Patel *et al*. 2006). General dental practitioners have been left to acquire this expertise without the aid of any systematic postgraduate training and guidance, in spite of the very unique multi-skill-dependent nature of this discipline.

In order to standardize and improve the delivery of Endodontic teaching, curricular guidelines for undergraduate Endodontics in USA (American Association of Dental Schools 1986) and in Europe (European Society of Endodontology 1992, 2001) have been made available. The scope of teaching was designed to embrace the quality guidelines laid by the European Society of Endodontology (ESE) (European Society of Endodontology 2004, 2006). Although there has been promising improvement in the delivery of undergraduate endodontic teaching in the UK since these guidelines were published (Qualtrough & Dummer 1997, Manogue *et al*. 1999), the priority given to the teaching of endodontics in UK has still been limited in the international context (Qualtrough *et al*. 1999). Most of the staff involved in teaching had no specialist training in the subject and some important topics were not taught (Qualtrough & Dummer 1997, McColl *et al*. 1999). The technical quality of root canal treatment completed by undergraduate students remained unsatisfactory (Hayes *et al*. 2001, Barrieshi-Nusair *et al*. 2004, Lynch & Burke 2006), particularly in molar teeth (Eleftheriadis & Lambrianidis 2005). The recent introduction of engine-driven canal preparation techniques (Hänni *et al*. 2003, Arbab-Chirani & Vulcain 2004) and the use of operating microscope (Rampado *et al*. 2004) in undergraduate programmes may potentially improve the technical quality of treatment (Peru *et al*. 2006).

After qualification, some general dentists in UK used the taught techniques but a larger percentage neither used rubber dam isolation nor solution with antibacterial and tissue dissolving properties for canal irrigation (Whitworth *et al*. 2000, Jenkins *et al*. 2001, Stewardson 2002, Lynch & McConnell 2007). They did, however, use techniques which had no evidence of clinical effectiveness and were not taught in undergraduate programmes (Jenkins *et al*. 2001). The problem of not following quality guidelines for Endodontic treatment was also found to be prevalent amongst Flemish dentists (Slaus & Bottenberg 2002). Evidence of improvement amongst dentists attending peer review sessions as part of the Belgian accreditation system has been reported (Hommez *et al*. 2003a&b). The rate of good quality of root fillings placed by a group of general dental practitioners in Sweden has also been reported to have increased after the introduction of the nickel-titanium rotary instrumentation technique (Molander *et al*. 2007a). Data shows that the manual use of new nickel-titanium instruments was popular amongst dentists (upto 50%) in Belgium and Copenhagen (Slaus & Bottenberg 2002, Hommez *et al*. 2003a, Bjørndal & Reit 2005). Their rotary versions were found to be less commonly (upto 22%) used (Parashos & Messer 2004, Bjørndal & Reit 2005). The long-term effect of the introduction of nickel-titanium instrumentation on the quality and outcome of root canal treatment delivered by general dental practitioners remains to be seen.

1.8 Prevalence of periradicular disease, root canal treatment and its quality

The teaching of endodontics in individual countries should fulfill the service demand from the corresponding population. Unfortunately, the quality of epidemiological data on endodontic treatment need from different populations varies. Periradicular disease is almost three-times more prevalent in contemporaneous than in prehistoric populations in France, despite the fact that the latter had no access to conservative dental treatment (Chazel *et al*. 2005). Restorative dental treatments may have detrimental impact on the health of pulpal and periapical tissues. When the predictive factors for periradicular disease from different periods were investigated using multivariable logistic regression, tooth wear (Chazel *et al*. 2005) and caries were major risk factors (Chazel *et al*. 2005, Kirkevang & Wenzel 2003) but age did not seem to be influential (Chazel *et al*. 2005, Frisk & Hakeberg 2005). Recently, smoking has been reported as a potential risk factor for periapical periodontitis from a cross-sectional study (Kirkevang & Wenzel 2003).

The prevalence of periapical disease in the modern age ranges from 0.6% in Norway (Eriksen *et al*. 1995) to 14% in Greece (Georgopoulou *et al*. 2005), of the remaining teeth present in individuals of different populations. The large variation may reflect the different oral health education/service systems in various countries but may more likely be related to the differences in the characteristics of the sample population and the method for screening. In most of the previous studies, the sample population was recruited from patients seeking treatment at dental schools who may represent a biased group (Saunders *et al*. 1997, Schulte *et al*. 1998, DeMoor *et al*. 2000, Boucher *et al*. 2002, Hommez *et al*. 2002, Jiménez-Pinzón *et al*. 2002, Lupi-Pegurier *et al*. 2002, Boltacz-Rzepkowska & Pawlicka 2003, Dugas *et al*. 2003, Georgopoulou *et al*. 2005, Kabak & Abbott 2005, Siqueira *et al*. 2005, Tsuneishi *et al*. 2005, Sunay *et al*. 2007, Touré *et al*. 2008). The prevalence of periradicular disease might have been over-estimated in these studies when compared with the findings from studies in which the samples were randomly selected from central bureau registrations (Eriksen *et al*. 1988a, 1995, Petersson *et al*. 1986, 1991, 1993, Odesjo 1990, Marques *et al*. 1998, Sidaravicius *et al*. 1999, Kirkevang *et al*. 2000, 2001a). On the other hand, the prevalence of disease might have been under-estimated if a dental panoramic tomograph alone was used for lesion detection (Gröndahl *et al*. 1970). Although lesion detection in the maxillary molar region could be enhanced using panoramic tomographs (Valachovic *et al*. 1986), small periapical changes (Muhammed & Manson-Hing 1982) or lesions in the maxillary anterior regions (Gröndahl *et al*. 1970) are difficult to visualize on dental panoramic tomographs.

Globally, pulpal and periradicular diseases and their management constitute a high proportion of problems in the general dental practice (Callis *et al*. 1993, Ellis *et al*. 2001, Hull *et al*. 2003). There was a steady increase in the level of root canal treatment from 1966 to 1986 (Farrell & Burke 1989) in the UK. In 1992, over £43 million were spent on root canal treatment in the general dental services of the National Health Service in UK (Dental Practice Board 2005). This trend has been relatively consistent since but does not take account of the increasing amount of care provided privately and by specialist endodontists. In the San Antonio area in USA, a total of 3672 teeth in 3350 military servicemen and their direct family members required root canal treatment during an 8-year period (1984–1992) (Wayman *et al.* 1994). A more recent study revealed Endodontic services constituted approximately 2% of all dental procedures performed in Florida, USA (Boykin *et al.* 2003). Similarly, there was also a significant increase in endodontic treatment need of 17% per 1000 patients over three decades (1977–2003) observed amongst the low caries rate Danish adult population (Bjørndal & Reit 2004). The increase in Endodontic treatments was probably related to fewer tooth extractions. With the introduction of postgraduate Endodontic training programmes in USA, most of the more complex procedures such as root canal treatment on molar teeth, non-surgical retreatment and surgical treatment has been carried out by specialist endodontists (Hull *et al.* 2003).

Despite the improvements in Endodontic training and increase in provision of Endodontic treatment, the reasonably robust epidemiological data from Scandinavian countries (Eckerbom *et al.* 1987, 1989, 1991, 1992, 2007, Eriksen *et al.* 1988a, 1995, Allard & Palmqvist 1986, Bergström *et al.* 1987, Petersson *et al.* 1986, 1989, 1991, Petersson 1993, Odesjö 1990, Eriksen & Bjerness 1991, Soikkonen 1995, Kirkevang *et al.* 2000, 2001a) suggest a high proportion of untreated lesions (up to 57%) and a high proportion of root treated teeth (up to 38%) associated with radiographic evidence of "persistent" periapical lesions. These trends remained consistent over time (Eckerbom *et al.* 2007) and endodontic problems have been found to be the main cause of tooth extractions (Eckerbom *et al.* 1992, Petersson *et al.* 1991). Although some of these periapical lesions might be in the process of healing following treatment, a large percentage may potentially require re-treatment in the future. Similar to the data from Scandinavian countries, the prevalence of untreated lesions in most other countries (Canada, Greece, France, Germany, Switzerland, Turkey, UK, and USA) ranged between 30% to 60% (Imfeld 1991, Buckley & Spångberg 1995, Saunders *et al.* 1997, Weiger *et al.* 1997, Dugas *et al.* 2003, Chazel *et al.* 2005, Georgopoulou *et al.* 2005, Sunay *et al.* 2007, Gulsahi *et al.* 2008). This figure was however, the lowest for Japan (13%) (Tsuneishi *et al.* 2005) and highest for Senegal (89%) (Touré *et al.* 2008). The low prevalence of untreated lesions in Japan may be attributed to the high dentist-to-population ratio, compulsory oral health care insurance system and the relatively low cost of Endodontic treatment (Tsuneishi *et al.* 2005). This may explain the high prevalence of root filled teeth in this country when compared with other European and American countries (Buckley & Spångberg 1995, Eckerbom *et al.* 2007).

The presence of persistent periapical lesions associated with root treated teeth was positively correlated with technically suboptimal root fillings, that were not compliant with guideline quality standards (Kirkevang *et al.* 2000, Kirkevang *et al.* 2001a, Boucher *et al.* 2002, Lupi-Pegurier *et al.* 2002, Boltacz-Rzepkowska & Pawlicka 2003, Hommez *et al.* 2002, Dugas *et al.* 2003, Seguta-Egea *et al.* 2004, Loftus *et al.* 2005, Kabak & Abbott 2005, Sunay *et al.* 2007, Touré *et al.* 2008) and with the poor quality of coronal restorations (Ray & Trope 1995, Kirkevang *et al.* 2000, Hommez *et al.* 2002, Dugas *et al.* 2003, Seguta-Egea *et al.* 2004).

Unfortunately, there has been no evidence of improvement in the quality of root fillings over the last few decades in most countries (Eckerbom *et al.* 1987, 1989, 1991, 1992, 2008, Eriksen *et al.* 1988a, 1995, Schulte *et al.* 1998), except in Denmark (Kirkevang *et al.* 2001b). Definitive conclusions on the influence of quality of root filling and coronal restoration on persistent periradicular disease may only be drawn from longitudinal clinical outcome studies.

1.9 Outcome of root canal treatment

The earliest systematic reports on the outcome of root canal treatment were presented by the visionary clinicians (Hinman 1921, Blayney 1922, Rhein 1926, Grove 1926, Puterbaugh 1926, Coolidge 1927, Buchbinder 1936, Auerbach 1938) who opposed the focal infection theory and acted as the custodians of the practice. Since 1921, over one hundred articles have been written on the clinical outcome of primary or secondary root canal treatment. Substantially more studies on primary treatment have been published than on secondary treatment.

1.9.1 Overview of methodological characteristics of previous studies

1.9.1.1 Type of studies

Clinical research may be classified into two broad types of study design: (1) intervention; or (2) observational; with further sub-division into prospective and retrospective. Retrospective studies can be further sub-divided into longitudinal and cross-sectional designs (Altman 1991). An interventional clinical study is effectively a clinical trial with data collected prospectively and longitudinally. The researcher deliberately influences events and investigates the effects of the intervention by controlling or varying the experimental condition. Depending upon design and execution quality, strong inferences can be drawn from such trials, with the evidence regarded at the highest level (Altman 1991). The level may however drop to the lowest rank if the study fails to provide a conclusive answer because of wide confidence intervals (Phillips *et al.* 1998) (Appendix I).

Where the factors under investigation cannot be controlled, the observational design is used (Altman 1991). The goal of an observational study is nevertheless to derive the same truth that would putatively have been obtained from an experimental trial (Gray-Donald & Kramer 1988). Prospective cohort studies (also called follow-up or longitudinal studies) which follow patients forward in time, are the method of choice for investigation of causal factors. It is also possible to conduct a historical cohort study, in which a previously existing cohort is identified, and their experience up to the present is measured. However, the likelihood of missing relevant data is high in this type of study. Although prospective cohort studies are time-consuming, expensive and may not be suitable for study of rare outcomes, they are less prone to bias when compared with retrospective case-control or cross-sectional studies (Breslow & Day 1987).

Case-control studies run backwards in time by comparing a number of subjects (the cases) with the event in question and those subjects without the event (controls).

The past history of the two groups in relation to the exposure(s) of interest is then compared. However, the method is prone to bias due to selection of an inappropriate control group which differs in other ways from the case group and in particular may be atypical with regard to the exposure of interest (Roberts *et al.* 1978). Other sources of bias include differential recall by cases and controls (Mackenzie & Lippman 1989), inaccuracy and incompleteness of retrospective data obtained from medical records (Breslow & Day 1987), and detection bias related to more frequent screening for patients with particular conditions (Altman 1991).

Cross-sectional studies, in contrast collect information on exposure to factors and event of interest within a given timeframe without knowledge of their temporal relationship; therefore only an association between the factors and event of interest may be revealed (Eriksen *et al.* 2002).

Of the studies identified on primary root canal treatment outcome, only ten were randomised trials investigating the influence of different aspects of the procedure on outcomes (Table 1.9.1 – Overleaf). Most of the previous trials did not fully satisfy the consolidated standards on reporting trials (CONSORT statement) (Altman *et al.* 2001) (Table 1.9.2, page 43). Secondary root canal treatment procedures have never been compared in randomized controlled trials.

For investigating the effect of pre-operative prognostic factors, the prospective cohort study design has been used by only a small proportion of previous studies (Sjögren *et al.* 1990, Byström *et al.* 1987, Ørstavik *et al.* 1987, Hoskinson *et al.* 2002, Farzaneh *et al.* 2004a&b) whilst most of the rest have been retrospective studies. Given the difference in the nature of infection between previously untreated and root-filled teeth (Gulabivala 2004a), the outcome of primary and secondary root canal treatments and their prognostic factors may be different. It may therefore be more appropriate to analyse the outcome data for the two types of treatment separately. Unfortunately, most of the data on secondary treatment have been presented and analysed together with the data on primary treatment (Grahnén & Hansen 1961, Storms 1969, Selden 1974, Heling & Kischinovsky 1979, Pekruhn 1986, Sjögren *et al.* 1990, Friedman *et al.* 1995, Chugal *et al.* 2001, Hoskinson *et al.* 2002, Fouad & Burleson 2003, Spili *et al.* 2004, Imura *et al.* 2007) or surgical re-treatment (Allen *et al.* 1989). In most of these studies, secondary treatment only represented a small proportion of their total sample (Grahnén & Hansson 1961, Pekruhn 1986, Molven & Halse 1988, Sjögren *et al.* 1990, Friedman *et al.* 1995, Chugal *et al.* 2001, Hoskinson *et al.* 2001). Only a few studies (Bergenholtz *et al.* 1979a&b, Van Nieuwenhuysen *et al.* 1994, Danin *et al.* 1996, Sundqvist *et al.* 1998, Farzahneh *et al.* 2004b, Gorni & Gagliani 2004, de Chevigny *et al.* 2008b) have been specifically designed to investigate secondary root canal treatment. None of the previous studies has investigated whether the direction and magnitude of the effect of potential prognostic factors are different for primary and secondary treatment. In order to do so, similar numbers of cases should be investigated from the two types of treatment.

Table 1.9.1 Quality of previous randomized controlled trials on root canal treatment procedures

Study	Intervention compared	Sample size estimation	Randomization method	Evidence of Concealment	Blinded patient	Assessor	Blinded assessor
Ørstavik *et al*. (1987)	Three types of sealer (AH 26®, Protosol, Kloropercha)	No	Throwing a die	No	No	Not operators	Yes
Reid *et al*. (1992)	Root filling materials (Hydron® and gutta-percha with AH26® sealer)						
Trope *et al*. (1999)	Single-visit and two-visit treatment (With and without calcium hydroxide dressing in two-visit group)	Power=0.8, significance level not reported, Clinical difference = 5%	Throwing a die	No	No	Not operators	Yes
Weiger *et al*. (2000)	Single-visit and two-visit treatment	No	Flipping a coin by operator	No	No	Operators	No
Pettiette *et al*. (2001)	Use of stainless steel ad nickel-titanium hand files for canal preparation	No	Flipping a coin by operator	No	No	Unknown	No
Peters & Wesselink (2002)	Single-visit and two-visit treatment	No	Every other patient	No	No	Not operators	Yes
Huumonen *et al*. (2003)	Three types of sealer (AH 26, Protosol, Kloropercha)	No	Flipping a coin by operator	No	No	Not operators	No
Gesi *et al*. (2006)	Single-visit and two-visit treatment	No	Flipping a coin by operator	No	No	Not operators	Yes
Molander *et al*. (2007b)	Single-visit and two-visit treatment	No	Flipping a coin by operator	No	No	Unknown	No
Penesis *et al*. (2008)	Single-visit and two-visit treatment	Power=0.8, $p<0.05$, Clinical difference = 0.5 unit of PAI	Block of random number	Yes	No	Not operators	Yes

Table 1.9.2 CONSORT checklist items to include when reporting a randomized trial (Altman *et al*. 2001)

Paper section and topic	Item number	Descriptor
Title and abstract	1	How participants were allocated to interventions (e.g., "random allocation", randomized" or "randomly assigned").
Introduction		
Background	2	Scientific background and explanation of rationale.
Methods		
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.
Objectives	5	Specific objectives and hypotheses.
Outcomes	6	Clearly defined primary and secondary outcome measure and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).
Sample size	7	How sample size was determined and when applicable, explanation of any interim analyses and stopping rules.
Randomization		
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification).
Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment, If done, how the success of blinding was evaluated.
Statistical method	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.
Results		
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome, Describe protocol deviations from study as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.
Baseline data	15	Baseline demographic and clinical characteristics of each group.
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat". State the results in absolute numbers when feasible (e.g. 10 of 20, not 50%).
Outcome and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% confidence interval).
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.
Adverse events	19	All important adverse events or side effects in each intervention group.
Discussion		
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.
Generalisability	21	Generalisability (external validity) of the trial findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

1.9.1.2 Outcome measures and criteria for successful treatment

The outcome of primary and secondary root canal treatments has been assessed using different measures depending on the perceived outcome of importance for researchers, dentists or patients. Academic researchers interested in identifying the prognostic factors, have tended to opt for radiographic and clinical signs of resolution of periapical disease (Friedman 2002). From the patient's perspective, the measures of utility have included resolution of symptoms (Bender *et al*. 1966a&b), functionality of the tooth (Friedman & Mor 2004) and quality of life (Dugas *et al*. 2002). For the health planning professional or dental insurance companies, survival of the root canal fillings/treatment (Cheung 2002, Cheung & Chan

(2003, Stoll *et al*. 2005, Lumley *et al*. 2008, Tickle *et al*. 2008) and tooth retention/survival (Lazarski *et al*. 2001, Salehrabi & Rotstein 2004) may be the most interesting outcome.

Traditionally, the two-dimensional image of periapical radiographs has been a well accepted method for assessment of the periapical status of teeth following endodontic treatment. With the development of digital imaging technology and digital intra-oral radiography in the 1980s (Gratt *et al*. 1980), a number of variations on detection of periapical changes have been explored. They included digital subtraction radiography (Tyndall *et al*. 1990, Ørstavik *et al*. 1990, Delano *et al*. 1998, Yoshioka *et al*. 2002), densitometric image analysis (Ørstavik 1991), and image processing by correction of gray values (Camps *et al*. 2004) or brightness & contrast (Gesi *et al*. 2006).

Digital subtraction radiography, however, theoretically requires absolute standardization of image geometry, contrast and blackening of the image. Discrepancy in geometry of two radiographic images is unavoidable despite use of a beam-aiming device together with a customized bite block (Ørstavik *et al*. 1990, Yoshioka *et al*. 2002). The accuracy of such bite blocks deteriorate with time due to a combination of physiologic tooth movement and deformation of the bite block (Yoshioka *et al*. 2002). Nicopoulou-Karayianni *et al*. (2002) and Mikrogeorgis *et al*. (2004) used a compensation technique involving translation, rotation and vertical angulation changes of the images by image transformation; they concluded that the method has sufficient accuracy and reliability as well as giving better observer agreement. Image transformation could not overcome the problem of superimposition of root apex by other anatomical structures.

Densitometric image analysis may facilitate objective determination of periapical lesion healing by comparing the ratio of gray values of healthy and diseased periapical areas immediately after treatment and at follow-up (Ørstavik *et al*. 1990). Signs of healing could be detected earlier when using this approach compared with the conventional approach (Ørstavik *et al*. 1990). This method is well accepted; particularly when the primary data is digital (Pettiette *et al*. 2001) rather than secondary digitisation of conventional radiographic images. Despite the positive reports, errors may still be introduced during the manual outlining of periapical lesions as distinct from adjacent healthy tissue. Therefore, although the data comparison is potentially objective, the data definition is prone to subjectivity. Therefore the use of a single observer in analysing such data (Delano *et al*. 2001) is questionable.

Many studies only considered the threshold of treatment success to be passed when both radiographic and clinical examination revealed an absence of periapical disease (Friedman & Mor 2004). A small proportion of cases may present with persistent symptoms despite apparent complete resolution of the periapical radiolucent lesion (Polycarpou *et al*. 2005). A comparison of such success rates estimated with or without clinical examination revealed no difference (Hoskinson *et al*. 2002). Interestingly, presentation of pain has only been used as an outcome measure in studies following up cases for 1 month (Yesiloy *et al*. 1988, Albashaireh & Alnegrish 1998, Oginni 2004, Yoldas *et al*. 2004).

The definitions for success and failure suggested by Strindberg (1956) were based on both radiographic and clinical findings and have been widely adopted or adapted in many studies (Grahnén & Hansson 1961, Sjögren *et al*. 1990, Chugal *et al*. 2001, Khedmat *et al*. 2004, Spili *et al*. 2004, Molander *et al*. 2007b) (Table 1.9.3). Friedman & Mor (2004) were sceptical about using the terms "success" and "failure" because their "ambiguity" could confuse patients. They have therefore labelled their outcomes as: healed, healing and diseased. In table 1.9.3, the "healed" category corresponds to the "success" category defined by Strindberg (1956); whilst the "healing" category corresponds to the "success" category described by Bender *et al*. (1966a&b).

Criteria demanding that success only be designated upon complete resolution of periapical radiolucency could be described as a "strict" threshold. Conversely, the term "loose" threshold could be applied to acceptance of merely a reduction in size of periapical radiolucency as success (Bender *et al*. 1966a&b) (Table 1.9.3). The same principle of designation was used by Friedman & Mor (2004), though they used the synonymous terms "lenient" and "stringent" to describe the thresholds. The frequency of adoption of these two sets of criteria in previous studies has been similar; the expected success rates using "strict" criteria would be lower than those based on "loose" criteria. The literature finds the difference to vary from 4% to 48% (Friedman 2002).

Table 1.9.3 Criteria for determination of periapical status

Strindberg (1956)	Bender *et al*. (1966a&b)	Friedman & Mor (2004)
Success: ***Clinical****:* No symptoms ***Radiographic:*** The contours, width and structure of the periodontal margin were normal, or The periodontal contours were widened mainly around the excess filling.	**Success:** ***Clinical:*** Absence of pain / swelling Disappearance of fistula No loss of function No evidence of tissue destruction ***Radiographic:*** An eliminated or arrested area of rarefaction after a post-treatment interval of 6 months to 2 years	**Healed:** ***Clinical:*** Normal presentation ***Radiographic:*** Normal presentation
Failure: ***Clinical:*** Presence of symptoms ***Radiographic:*** A decrease in the periradicular rarefaction, or Unchanged periradicular rarefaction, or An appearance of new rarefaction or an increase in the initial rarefaction.		**Diseased:** Radiolucency has emerged or persisted without change, even when the clinical presentation is normal, or Clinical signs or symptoms are present, even if the radiographic presentation is normal.
Uncertain: ***Radiographic:*** There were ambiguous or technically unsatisfactory control radiographs which could not for some reason be repeated; or The tooth was extracted prior to the 3-year follow-up owing to the unsuccessful treatment of another root of the tooth.		**Healing:** ***Clinical:*** Normal presentation ***Radiographic:*** Reduced radiolucency.

When using the periapical index (PAI, previously discussed on pages 27–29), earlier studies (Ørstavik & Hörsted-Bindslev 1993, Ørstavik 1996) only reported of increase or decrease in mean scores for the factors under investigation, with reporting the proportion of cases successful. In other studies, the PAI scores were dichotomized into "healthy" (PAI 1 or 2) or "diseased" (PAI 3–5) periapical tissues (Ørstavik *et al*. 1987, Penesis *et al*. 2008), allowing this data to be compared directly with more traditionally used binary outcomes of success or failure. In this system of designation, given that the periodontal ligament space is slightly widened in score PAI 2, it effectively signals the adoption of a "loose" criterion. Recent analyses (Halse & Molven 2004) of 14 cases presenting with widened apical periodontal ligament space (PAI score at 2) at 10–17 years post-operatively, revealed that the widening may represent unfavourable future healing in a proportion (28%, 4/14), when followed-up for another 10 years.

Recently, another outcome measure, "functional retention", has been introduced as an independent outcome measure (Friedman & Mor 2004), to aid direct comparison between outcomes of endodontic treatment and tooth extraction followed by implant replacement. A tooth was judged "functional" after treatment when there was absence of clinical signs and symptoms, regardless of the presence or absence of periradicular radiolucency. Not surprisingly, all the studies using this outcome measure originated from Friedman's group (Friedman *et al*. 2003, Farzaheh *et al*. 2004a&b). The effects of various prognostic factors on this outcome measure have never been determined.

"Survival of teeth after root canal treatment" is a similar but more lenient outcome measure than "functional retention", as it ignores the clinical condition of teeth at recall. The perceived "threat" to endodontic treatment from the competing treatment option (extraction & implant supported prosthesis) has popularized the study of "tooth survival" (Lazarski *et al*. 2001, Caplan *et al.* 2002, Dammaschke *et al*. 2003, Alley *et al*. 2004, Lynch et al. 2004, Salehrabi & Rotstein 2004, Tilashalski *et al*. 2004, Caplan *et al*. 2005, Nagasiri *et al*. 2005, Stoll *et al*. 2005, Tan *et al*. 2006, Salvi *et al*. 2007, Chen *et al*. 2008). Apart from tooth extraction, other competing outcomes such as tooth undergoing further non-surgical or surgical treatment may also be considered failure events (Stoll *et al*. 2005, Tickle *et al*. 2008, Lumley *et al*. 2008).

More rarely used dimensions of root canal treatment outcome are "quality of life" and "patient satisfaction" (Dugas *et al*. 2002). They found that the quality of life of patients was found to improve significantly after endodontic treatment as a result of pain relief and allowed return to normal sleep patterns.

1.9.1.3 Unit of outcome assessment

Either tooth or root, or sometimes both have frequently been used as the unit for assessing the outcome (Friedman 2002). "Patient" has only been used as a unit when "quality of life" and "patient satisfaction" were assessed (Dugas *et al*. 2002). Given that often it is considered clinically appropriate to repeat the root canal treatment on the entire tooth or extract the entire tooth when problems persist after root canal treatment, it has often been considered more appropriate to use "tooth" as the unit of measure. In truth, multi-rooted teeth may be selectively treated by root-end surgery, root-resection or hemi-section to manage individual root(s) with persistent problems.

The issue of unit of assessment may be critical when determining the effect of root-level prognostic factors for resolution of apical periodontitis; use of tooth as the unit assessment would confound such analyses. Another effect of unit of assessment is its potential influence in over-estimated success when multi-rooted teeth are included in the sample and root is used as the unit of assessment (Friedman 2002). A study providing simultaneous outcomes for both units of assessment did not support this speculation, the success rate estimated by tooth as a unit was only 3% higher than that using root as a unit, despite the fact that molar teeth constituted 80% of their sample (Hoskinson *et al.* 2002).

1.9.1.4 Duration after treatment and recall rate

There is an absence of standardization in the, "duration-after-treatment", when the outcomes should be reviewed; previous studies have adopted time intervals ranging from 6 months (Seltzer *et al.* 1963) to 27 years (Fristad *et al.* 2004). The European Society of Endodontology's Quality Guidelines for Endodontics (2006), suggest a clinical and radiographic follow-up at least one year after treatment with subsequent annual recall for up to four years before a case is judged a failure. The American Association of Endodontists concurs with a suggestion of clinical and radiographic evaluation for up to five years. Consistent with recent trends they also added the proviso of determining the functionality of the treated tooth (http://www.aae.org/dentalpro/guidelines.htm). The origin of the "four year" standard is probably the work of Strindberg (1956) who reported that the stabilisation of periapical lesion healing was not observed until 3 years after the operation. Forty years later, Ørstavik (1996) reported the peak incidence of healing to be at 1 year. Almost ten years earlier, Byström *et al.* (1987) had reported on the healing dynamics and noted that the size of completely healed lesions had decreased to about 2 mm within 2 years, regardless of the initial size. From a research perspective, this means that cases should be reviewed following treatment, for a minimum of 1 year if loose criteria for success are to be used but preferably for at least 3 years if strict criteria for success are to be used. It would be preferable to standardize the duration after treatment for all the patients or at least to include the duration as a covariate into the statistical model to account for any variations in the success rate due to the different follow-up times.

The reality is that the longer the duration of follow-up after treatment, the lower the recall rate; the literature reveals this to range from 11% (Selden 1974) to 100% (Peters & Wesselink 2002). Although there is no specific level of loss to follow-up at which attrition-related bias becomes acknowledged as a problem (Dumville *et al.* 2006), the possibility of bias should become a concern when the loss to follow-up is 20% or more in a randomized controlled trial (Schulz & Grimes 2002). This is particularly so when there is a significant difference in the drop-out rate between the two arms of a trial (Dumville *et al.* 2006). There is however, no equivalent discussion related to longitudinal observational studies.

The use of financial incentives may help improve recall rates in a cohort study (Wang *et al.* 2004). Other strategies for improving recall rates in clinical trials or cohort studies have not been reported, although such data are available for new appointment attendances. Common reasons given for failure to keep a new appointment include lack of awareness of the appointment (Grover *et al.* 1983) or forgetfulness (O'Brien & Lazebnik 1998). In addition to the reduction in the length of the elapsed interval between making the appointment and the visit day (O'Brien & Lazebnik 1998), the attendance rates could also be improved by a telephone or letter reminder prior to the appointment (Grover *et al.* 1983, O'Brien & Lazebnik 1998). Although telephone calls were more effective than letter reminders, the latter were considered more cost-effective (Shepard & Moseley 1976). Telephone calls have the further advantage of allowing the health worker to reinforce the purpose of the appointment as well as to answer legitimate queries in person (Shepard & Moseley 1976). Other factors influencing clinic attendance were patient perception of the staff attitudes toward them, continuity of the providers, waiting time in the clinic, as well as appearance and hygiene of the clinic environment (Bigby *et al.* 1983, Rust *et al.* 1995).

1.9.1.5 Statistical methods for investigation of prognostic factors

One of the most common design problems in medical research is that the sample size is too small with inadequate power to detect an important effect if one exists (Freiman *et al.* 1978). Unless the true treatment effect is large, small trials can yield a statistically significant result only by chance or if the observed difference in the sample is much larger than the real difference (Altman 1999). The statistical method for calculating the appropriate sample size is based on the power required of a hypothesis test and the specified smallest true difference between the two conditions/interventions under investigation that would be clinically valuable (Altman 1999). The latter is however, artificial and difficult to define (Altman 1999). The greater the power of the test, the greater the certainty that the outcome represents the truth, but this requires a larger sample. Amongst the clinical outcome studies on root canal treatment, the use of power calculation for determination of sample size has only been reported occasionally (Trope *et al.* 1999, Farzaneh *et al.* 2004a, Penesis *et al.* 2008).

When analysing the association between potential influencing factors and treatment outcome, the occurrence of confounding can produce spurious effects such as hiding, reducing the true effects of a genuine prognostic factor or magnifying the effect of a dubious factor (Grimes & Schulz 2002). For confounding to occur, the variable of interest must be associated with the confounder which must in turn be associated with the outcome. However, most studies on root canal treatment outcome have not considered the effects of potential confounders. In addition, the hierarchical structure of the Endodontic dataset is mostly ignored. By this is meant that multiple roots are nested within the same tooth, and multiple teeth are nested within the same patients. The units within each cluster cannot be considered independent to each other. In addition, the prognostic factors for the outcome of root canal treatment may operate at individual root, tooth or subject levels. At these different levels, the relationship between a prognostic factor and treatment outcome might be attenuated by different confounder profiles. Thus, prognostic factors may play different roles in predicting outcome at these three levels (Mancl *et al.* 2000). The hierarchical structure of the data may only be accounted for by a multi-level or random effects modelling approach (Mancl *et al.* 2000, Tu *et al.* 2004a&b) or marginal effect models with robust standard errors and/or generalised estimating equations (Hoskinson *et al.* 2002). In dentistry, a random effect model was adopted for analysis of continuous periodontal data; the literature search revealed no other examples.

The most commonly used statistical method for analysing the binary outcome (success/failure) of root canal treatment was the chi-squared test (Friedman 2002). This test is capable of investigating each potential factor individually; under such conditions, the confounding could only be addressed by carrying out summary measures for each cluster but this may compromise the statistical power. A multivariable regression analysis which can account for the confounding is therefore a more appropriate method for analysing such complex clinical data (Grimes & Schulz 2002).

Determining the time to healing of periapical lesions (success) by survival analysis techniques would seem to be a logical approach, but it requires *frequent regular* radiographic follow-up of all patients in order to record the exact time of complete disappearance of a lesion. The problem of interval censoring is that the time of failure cannot be precisely defined (Cheung 2002, Cheung & Chan 2003). Ultimately they compromised by estimating the time to failure as the mid-point between the date of failure recognition and the date of previous follow-up examination. This strategy, although well accepted by statisticians (Finkelstein 1986), would only hold true under the following biological assumption: that failure is always preceded by a phase of healing after treatment. Otherwise, the case is failing from the moment of treatment completion, the ambiguity merely residing in the ability to identify this fact early. Once so identified, the moment of failure must be time zero. On the positive side, the survival analysis method has the capability to reduce the bias due to drop-outs by “right censoring”, if loss to follow-up is uninformative (unrelated to the failure of the tooth). This method also enables competing outcomes to be investigated appropriately. Survival analysis has been used by a number of studies to evaluate the time to complete healing (Weiger *et al.* 2000), survival of root canal fillings (Stoll *et al.* 2005), survival of treatments measured by many competing outcomes (Cheung 2002, Cheung & Chan 2003) or tooth survival (Caplan & Weintraub 1997, Lazarski *et al*. 2001, Caplan *et al*. 2002, Dammaschke *et al*. 2003, Alley *et al*. 2004, Caplan *et al*. 2005, Nagasiri *et al*. 2005).

A number of the studies using the PAI for monitoring periapical status have compared the mean PAI scores pre-operatively and at post-operative follow-up using parametric Analysis of Variance (ANOVA) (Cvek 1972, Trope *et al*. 1999, Heling *et al*. 2001), non-parametric Friedman test/Mann-Whitney U test (Peters & Wesselink 2002, Huumonen *et al*. 2003) or "Relative to an identified distribution" (RIDIT) (Ørstavik *et al*. 1987, Eriksen *et al*. 1988b, Ørstavik 1996). The ANOVA method may be inappropriate for such analyses as the PAI is not a continuous variable with a normal distribution but an ordinal categorical variable with the increment of scores not directly in proportion to the increment in severity of periapical disease. RIDIT which was derived by Bross (1958) is a non-parametric method for analysing ordinal categorical outcome and has been rarely used recently. It was first applied in dental research to compare the marginal fracture of amalgam restorations, with fractures graded on a five-point (Mahler *et al*. 1970) or a six-point (Mahler *et al*. 1973) ordered scale.

When investigating the prognostic factors for tooth survival, one of the following methods of analysis were used: chi-square test (Alley *et al*. 2004, Lynch *et al*. 2004, Salehrabi & Rotstein 2004, Chen *et al*. 2008), life table, Kaplan-Meier curves with log-rank test (Mantel-Haenszel method) (Stoll *et al*. 2005, Lumley *et al*. 2008, Tickle *et al*. 2008). Only Caplan and colleagues (Caplan & Weintraub 1997, Aquilino & Caplan 2002, Caplan *et al*. 2002, Caplan *et al*. 2005) used multiple logistic or Cox regression models to account for the potential confounders for the factor of interest. Chi-square tests compare the proportion of events by the groups of subjects under investigation taking into account only those subjects who can be observed and without accounting for the effects of potential confounders, giving potentially biased estimates. Life table estimates and Kaplan-Meier curves provide information on the cumulative probability of survival in each group at different times after the starting point. The survival experiences of the group can then be compared using a log-rank test, also called Mantel-Haenszel test (Collet 2003). The major drawbacks of the log-rank test are that it does not give the size of the effect of a particular factor of interest and it does not account for any other factors that may affect the survival time. This latter drawback may be overcome by stratifying the data and using a stratified log-rank test. In more complicated cases, it is more appropriate to use a form of multivariable regression (e.g. Cox regression) where the survival is modelled through the hazard function or event rate (Cox 1972). One of the main assumptions underlying the Cox regression models is that the effect of a prognostic factor is constant over time (proportional hazards assumption). If the hazards cannot be assumed proportional then more advanced methods exist, the simplest being to stratify the analysis for the factor which violates proportionality (Collett 2003), however, the effect of this factor then, cannot be estimated. A more complicated approach is to split the dataset at time-points when the effect of a factor changes and include the modified effects of this factor (interaction with time-bands) into the model (Cleves *et al*. 2004).

1.9.2 Overview of prognostic factors for resolution of periapical disease by root canal treatment

The prognostic factors for resolution of periapical disease may be classified into pre-, intra- and post-operative factors and are discussed below.

1.9.2.1 Pre-operative factors

i) Gender

The majority of previous studies reporting on the influence of this factor on primary and secondary root canal treatment did not find any significant association between gender and success rate (Ingle 1965, Adenubi & Rule 1976, Jokinen *et al*. 1978, Oliet 1983, Swartz *et al*. 1983, Smith *et al*. 1993, Van Nieuwenhuysen *et al*. 1994, Friedman *et al*. 1995, Benenati & Khajotia 2002, Cheung 2002, Hoskinson *et al*. 2002, Cheung & Chan 2003, Fouad & Burleson 2003, Farzaneh *et al*. 2004a&b, Field *et al*. 2004, Khedmat *et al*. 2004, Spili *et al*. 2004, Imura *et al*. 2007, Zmener & Pameijer 2007). Swartz *et al*. (1983) & Smith *et al*. (1993) had independently reported root canal treatment in male patients to have significantly higher success rates than in female patients but their results were not adjusted and may have been confounded by other significant prognostic factors such as the presence of pre-operative periapical lesions.

ii) Age

The effect of age on treatment outcome has been analysed by evaluating age as a continuous variable (Hoskinson *et al*. 2002) or categorised by decade (Barbakow *et al*. 1980b, Swartz *et al*. 1983, Imura *et al*. 2007); or classified into 3 to 4 age bands (Grossman *et al*. 1964, Nelson 1982, Smith *et al*. 1993). The most commonly adopted strategy was to categorize age into 3 bands: up to 25 years, 25 to 50 years and above 50 years.

The patients' age was not found to have a significant influence on root canal treatment outcome in all but one study (Strindberg 1956, Seltzer *et al*. 1963, Ingle 1965, Harty *et al*. 1970, Barbakow 1980a&b & 1981, Nelson 1982, Oliet 1983, Swartz *et al*. 1983, Sjögren *et al*. 1990, Ørstavik & Hörsted-Bindslev 1993, Smith *et al*. 1993, Van Nieuwenhuysen *et al*. 1994, Friedman *et al*. 1995, Benenati & Khajotia 2002, Cheung 2002, Hoskinson *et al*. 2002, Fouad & Burleson 2003, Farzaneh *et al*. 2004a, Field *et al*. 2004, Khedmat *et al*. 2004, Spili *et al*. 2004, Chu *et al*. 2005, Zmener & Pameijer 2007). Imura *et al*. (2007) reported that age had a significant effect on the outcome of secondary but not primary treatment; the age group 50–59 was associated with highest success rate compared with other age bands pooled into one category. In their final multiple regression model, only one age band was analysed, the selection of which was data-driven without clinical basis. In fact, their summary data revealed no obvious trend, either linear or non-linear, in the success rates by different age bands.

Dichotomizing or categorizing continuous predictors is considered unnecessary and is unsupported on statistical grounds (Royston *et al*. 2006). The disadvantages include loss of information (such as detection of non-linear relationships with outcome), loss of statistical power, and increased probability of false positive results. The choice of cut-point should have a clinical basis or be consistent with previously recognized cut-points [Royston *et al*. 2006]. In the absence of a *priori* cut-point, the most common and acceptable approach is to take the sample median [Royston *et al*. 2006]. The arbitrariness of the choice of cut-point may lead to the idea of trying more than one value and choosing that which, in some sense, gives the most satisfactory result; it is worse still if the cut-points are selected using a data-dependent method [Royston *et al*. 2006]. The last strategy appeared to be adopted by Imura *et al*. (2007).

iii) General medical health

The effect of this factor on root canal treatment outcome has been poorly investigated. Some studies [Çalişken & Şen 1996, Trope *et al*. 1999, Peters & Wesselink 2002] reported that only healthy patients were included in their studies. Three studies [Markitziu & Heling 1981, Seto *et al*. 1985, Lilly *et al*. 1998] had investigated patients with a history of radiotherapy in the head and neck region and found success rates to be on par with healthy patients. One study used a "crude measure" of general health, against which to analyse treatment outcomes; they found no significant difference in the success rate of root canal treatment in "healthy" and "unhealthy" patients [Storms 1969].

Recently, specific medical conditions or habits with known medical associations: diabetes (non-insulin-dependent / insulin-dependent) [Fouad & Burleson 2003], impaired non-specific immune response [Marending *et al*. 2005] and smoking [Doyles *et al*. 2007] were found to significantly reduce the success rates of root canal treatment on teeth with periapical lesions. Using a four-category outcome measure (success/survival/survival-with-intervention/failure), Doyles *et al*. (2007) found that diabetes did not affect the outcome of primary root canal treatment, in contrast to Fouad & Burleson (2003) who had included cases with periodontal disease in their samples and used a binary outcome measure (success/failure). The outcome of root canal treatment on patients positive for the human immunodeficiency virus (HIV) (n=33) was compared with that on healthy patients (n=33) in a case-control study [Quesnell *et al*. 2005]; no significant difference was found at the 12-month follow-up. Other studies [Cooper 1993, Shetty *et al*. 2006, Suchina *et al*. 2006] have also confirmed that symptomatic clinical presentation, anti-retroviral therapy or viral load had no effect on root canal treatment outcome.

The overall intuitive impression, therefore, is that clinicians need not alter their expectations of healing and resolution of periradicular lesion based solely on health status, except in the exceptional circumstances mentioned above.

iv) Tooth type

There has been a wide variation in the manner of presentation of outcome data by tooth type in previous studies. The tooth descriptors or classifications used have included: maxillary/mandibular teeth; anterior/posterior teeth; anterior/premolar/molar; 1/2/3 roots; 1/≥2 canals; or designation of each tooth type.

Amongst the studies (Ingle 1965, Heling & Tamshe 1970 & 1971, Adenubi & Rule 1976, Seldon 1974, Jokinen *et al*. 1978, Barbakow 1980a&b & 1981, Oliet 1983, Morse *et al*. 1983a,b&c, Swartz *et al*. 1983, Pekruhn 1986, Allen *et al*. 1989, Ørstavik & Hörsted-Bindslev 1993, Peak 1994, Peretz *et al*. 1997, Benenati & Khajotia 2002, Cheung 2002, Hoskinson *et al*. 2002, Cheung & Chan 2003, Iqbal *et al*. 2003, Farzaneh *et al*. 2004a&b, Khedmat *et al*. 2004, Spili *et al*. 2004, Chu *et al*. 2005) that had investigated the influence of this factor on root canal treatment outcome, only a small proportion (Swartz *et al*. 1983, Smith *et al*. 1993, Benenati & Khajotia 2002, Cheung 2002, Cheung & Chan 2003, Field *et al*. 2004) found statistically significant differences in success rates of treatment between tooth types. Mandibular molars were found to have the lowest success rates (Swartz *et al*. 1983, Smith *et al*. 1993, Benenati & Khajotia 2002), whilst one study even localised this problem to the mandibular right quadrant (Smith *et al*. 1993). Furthermore, posterior teeth were associated with higher success rates than anterior teeth (Field *et al*. 2004). The results from four of these six studies were not adjusted for pre-operative lesion and other potential confounders; the two exceptions were Cheung (2002) and Cheung & Chan (2003). These 2 studies had analysed the survival of "treatment" using Cox regression analysis and found that molar teeth were associated with the worst survival outcome. Their definition of treatment failure had included "extraction of tooth", and "re-treatment of tooth", in addition to the presence of clinical and radiographic signs of periapical disease at follow-up.

v) Pulpal and periapical status

Previous reports on the effect of pre-operative pulpal status of teeth on root canal treatment outcome are contradictory. Vital teeth were found to have significantly higher success rates than non-vital teeth in some studies (Grahnén & Hansson 1961, Storms 1969, Smith *et al*. 1993, Hoskinson *et al*. 2002). Other studies, in contrast found no such difference (Strindberg 1956, Heling & Tamshe 1970 & 1971, Adenubi & Rule 1976, Barbakow 1980a&b & 1981, Nelson 1982, Morse *et al*. 1983a,b&c, Oliet 1983, Ørstavik & Hörsted-Bindslev 1993, Friedman *et al*. 1995, Cheung 2002, Zmener & Pameijer 2007). In a stark divergence from common findings, Teo *et al*. (1986) reported that non-vital teeth had significantly higher success rates than vital teeth with pulpitis. Closer inspection of their data revealed that some of their vital teeth had not received root canal treatment but pulpotomy or pulpectomy, rendering direct comparison of outcome invalid. Without dichotomising the periapical status of non-vital teeth, results of meta-analyses (Kojima *et al*. 2004) have confirmed that the effect of pulpal status was significant.

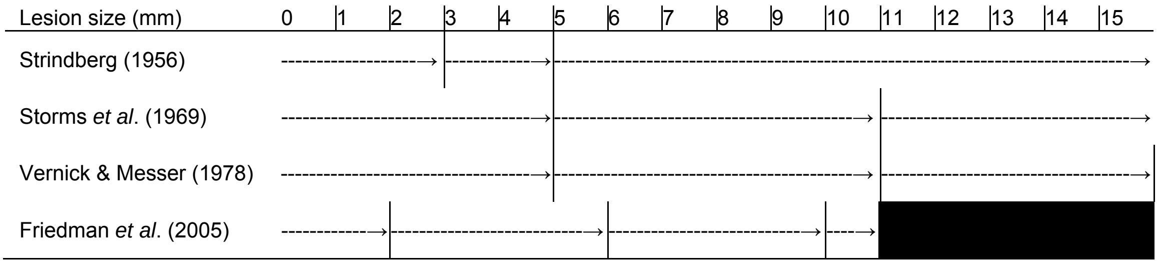
The previous history of root canal treatment on non-vital teeth may also influence root canal treatment outcome. There is a general belief that success rates for secondary root canal treatment are lower than those for primary treatment (Selden *et al.* 1974, Pekruhn 1986, Sjögren *et al.* 1990, Friedman *et al.* 1995) but this is not universally supported (Molven & Halse 1988, Chugal *et al.* 2001). As these studies were not specifically designed to address this question, the relatively small sample size for secondary treatment may explain the discrepancies.

In contrast to the conflicting reports on the effect of pulpal status, the findings on the effect of periapical status on root canal treatment outcome have been relatively consistent. Regardless of whether the analyses were conducted with (Engström *et al.* 1964, Heling & Tamshe 1970 & 1971, Adenubi & Rule 1976, Selden 1974, Jokinen *et al.* 1978, Morse *et al.* 1983 a, b & c, Swartz *et al.* 1983, Sjögren *et al.* 1990, Chugal *et al.* 2001, Hoskinson *et al.* 2002, Doyles *et al.* 2007, Molven & Halse 1988, Friedman *et al.* 1995, Hoskinson *et al.* 2002, Gorni & Gagliani 2004, Farzaneh *et al.* 2004b, Imura *et al.* 2007, de Chevigny *et al.* 2008b) or without (Strindberg 1956, Nelson 1982, Matsumoto *et al.* 1987, Halse & Molven 1987, Ørstavik & Hörsted-Bindser 1993, Smith *et al.* 1993, Friedman *et al.* 1995, Cheung & Chan 2003, Fouad & Burleson 2003, Farzaneh *et al.* 2004a, Spili *et al.* 2004, Negishi *et al.* 2005) controlling the pulpal status, teeth with a periapical lesion were associated with significantly lower success rates of root canal treatment than those teeth without a lesion. Some studies although revealing the same trend, found no statistically significant difference, which could be attributed to the lack of statistical power rather than a true effect (Cheung 2002, Peak 1994, Chu *et al.* 2005, Zmener & Pameijer 2007).

By pooling previous outcome data on periapical status without sub-stratifying for pulpal status, the significant effect of periapical status on root canal treatment outcome has been confirmed by meta-analyses (Kojima *et al.* 2004).

It may be important to consider how the data on periapical lesion size are handled when interpreting the reports on its effect on treatment outcome. Some studies consider periapical lesion size as a continuous variable (Chugal *et al.* 2002, Hoskinson *et al.* 2002, Sjögren *et al.* 1997), whilst others have categorized it into bands (Table 1.9.4). Despite the recording of lesion size by predetermined size bands, the analysis is sometimes further dichotomized for convenience. The thresholds for dichotomization have varied between 2 mm (Friedman *et al.* 1995, Zmener & Pameijer 2007) and 5 mm (Selden 1974, Sjögren *et al.* 1990, Matsumoto *et al.* 1987, Çalişkan *et al.* 2005) but none had justified their selection strategy.

Table 1.9.4 Examples of previous strategies for categorization of lesion size



Periapical lesion size has been found to have a significant influence on outcome of primary (Storms 1969, Selden 1974, Matsumoto *et al.* 1987, Friedman *et al.* 1995, Chugal *et al.* 2001, Hoskinson *et al*. 2002, Cheung & Chan 2003) and secondary (Bergenholtz 1979a&b, Van Nieuwenhuysen *et al*. 1994, Sundqvist *et al*. 1998) root canal treatment; with higher success rates for smaller than larger lesions. In contrast, others (Strindberg 1956, Byström *et al*. 1987, Sjögren *et al*. 1990, Danin *et al*. 1996, Sjögren *et al*. 1997, Çalişkan *et al*. 2005, Zmener & Pameijer 2007) have not found a statistically significant difference. The discrepancy in findings could be attributed to lack of statistical power in some studies, different criteria for success, and duration of follow-up. The sample sizes in three of the above studies (Danin *et al*. 1996, Çalişkan *et al*. 2005, Zmener & Pameijer 2007) were insufficient to detect a true effect. The intuitive impression that larger lesions may require longer to heal completely, tends to be corroborated by studies using strict criteria for outcome as well as an extended follow-up period, which found no difference in success rates (Strindberg 1956, Byström *et al*. 1987, Sjögren *et al*. 1990, Sjögren *et al*. 1997).

vi) Other pre-operative clinical signs and symptoms

Other conditions related to periapical status, which may influence root canal treatment outcome are presence of pre-operative pain (Friedman *et al*. 1995, Khedmat *et al*. 2004), sinus tract (Khedmat *et al*. 2004) and apical resorption (Strindberg 1956). Their presence has been found to significantly reduce the success of primary and secondary treatments. In contrast, Chugal *et al*. (2001) found the "presence of sinus" did not have any prognostic value when it was entered into a logistic regression model together with presence and size of periapical lesion. Similarly, the "Toronto study" (Friedman *et al*. 2003, Farzaneh *et al*. 2004a, Chevigny *et al*. 2008a) using multiple logistic regression analyses to account for confounding, and limiting their analyses to teeth with apical periodontitis, found that the presence of "pre-operative clinical signs and symptoms" did not influence primary root canal treatment outcome. Unfortunately, the "clinical signs and symptoms" investigated in the "Toronto study" were not clearly defined and their sample sizes were small.

vii) Time interval between primary treatment and retreatment (in secondary root canal treatment)

A persistent radiographic periapical radiolucency without any other clinical signs and symptoms after primary treatment may represent a healing lesion and cannot be regarded as treatment failure. The case for failure increases with such persistence after a follow-up duration of 3 years or more (Strindberg 1956). Thus it could reasonable to speculate that a long interval between primary and secondary treatment may compromise the success of the latter treatment. Two studies (Allen *et al*. 1989, Farzaneh *et al*. 2004b) had investigated the effect of this factor on outcome, but both concurred that there was no significant effect from this variable. Three other studies provided insight into this question by virtue of the fact that they limited inclusion of teeth to those that had received primary treatment at least 2 years (Bergenholtz 1979a&b, Çalişkan *et al*. 2005) or 4-5 years (Sundqvist *et al*. 1998) previously. Their reported success rates (75%, 62%, 74%, respectively) revealed no obvious trends. These results therefore suggested the above speculation was spurious.

viii) Pre-operative canal contents (in secondary root canal treatment)

The success rates of secondary root canal treatment related to the prior presence of different foreign materials in the root canal system had only been investigated in one study (Allen *et al.* 1989); their data however included surgical re-treatment cases (54% of the samples). The presence of pre-operative "cement" root fillings were associated with significantly lower success rates than teeth with "gutta-percha" or "silver point" root fillings. The outcome of secondary root canal treatment on teeth presenting with or without separated instruments, pre-operatively, has not been compared directly. However, Gorni & Gagliani (2004) reported that the success rate of treatment on teeth with pre-operative separated instruments was 96%, which was within the higher end of the range of reported success rates (88% – 97%) of primary treatment on teeth without apical periodontitis (Friedman & Mor 2004).

ix) Pre-operative procedural error in canal preparation (in secondary root canal treatment)

Pre-operative procedural errors may impede or complicate secondary treatment. The errors investigated have included: canal perforation, obstruction and "root canal morphology alteration by previous treatment", the latter defined as presence of transportation, perforation, stripping or internal resorption (Gorni & Gagliani 2004). The last condition was, obviously unrelated to the previous treatment. They found that success of secondary treatment was compromised if the root canal morphology was altered by the primary treatment (Gorni & Gagliani 2004).

A pre-existing perforation was found to compromise the outcome of secondary treatment significantly by the "Toronto study" (Farzaneh *et al.* 2004b, de Chevigny *et al.* 2008b), consistent with the low success rate for cases with perforation reported by Gorni & Gagliani (2004). In contrast, Main *et al.* (2004) reported that periradicular radiolucencies associated with perforations repaired with mineral trioxide aggregate cement (MTA®, Dentsply Maillefer) were completely resolved in all cases with pre-existing perforation. This finding was in agreement with the latest report from the "Toronto study" (de Chevigny *et al.* 2008b) comparing perforation repair with MTA® or glass ionomer cement.

x) Quality of pre-existing root fillings (in secondary root canal treatment)

Persisting apical disease associated with teeth containing radiographically adequate root fillings may be caused by intra-radicular infection, extra-radicular infection, a true cyst, or a foreign body reaction (Nair 2006). Of these, only the first would respond to secondary root canal treatment (Nair 2006). Studies (Danin *et al.* 1996, Farzaneh *et al.* 2004b, de Chevigny *et al.* 2008b) comparing the success rates of secondary root canal treatment on teeth with satisfactory versus unsatisfactory pre-existing root fillings have given conflicting reports. The first study found no significant influence by the apical extent of pre-existing root filling but only had a sample size of 18 teeth. Whereas the "Toronto study" (Farzaneh *et al*. 2004b, de Chevigny *et al*. 2008b) which only investigated teeth with pre-operative periapical lesion, found that the success rates for teeth with adequate pre-existing root fillings (extended to 0-2 mm from the radiographic root end with no voids) were significantly lower than those for teeth with inadequate pre-operative root fillings.

1.9.2.2 Intra-operative factors

i) Qualification of operators (undergraduate, postgraduate, general dental practitioner, specialist)

Published studies on root canal treatment outcome have involved operators of different qualification and skill mixes, they most frequently involved undergraduate students (Buchbinder 1936, Auerbach 1938, Buchbinder 1941, Morse & Yates 1941, Castagnola & Orlay 1952, Grahnén & Hansson 1961, Frostell 1963, Engström *et al*. 1964, Grossman *et al*. 1964, Engström & Lundberg 1965, Storms 1969, Heling & Tamshe 1970, Heling & Shapira 1978, Jokinen *et al*. 1978, Kerekes 1978, Vernieks & Messer 1978, Heling & Kischinovsky 1979, Kerekes & Tronstad 1979, Swartz *et al*. 1983, Byström *et al*. 1987, Halse & Molven 1987, Ørstavik *et al*. 1987, Safavi *et al*. 1987, Akerblom & Hasselgren 1988, Eriksen *et al*. 1988b, Sjögren *et al*. 1990, Ørstavik 1996, Pettiette *et al*. 2001, Benenati & Khajotia 2002) or specialists (Appleton 1932, Strindberg 1956, Seltzer *et al*. 1963, Zeldow & Ingle 1963, Bender *et al*. 1964, Oliet & Sorin 1969, Harty *et al*. 1970, Selden 1974, Werts 1975, Soltanoff 1978, Morse *et al*. 1983a,b&c, Oliet 1983, Ashkenaz 1984, Pekruhn 1986, Matsumoto *et al*. 1987, Shah 1988, Reid *et al*. 1992, Jurcak *et al*. 1993, Friedman *et al*. 1995, Çalişken & Şen 1996, Gutknecht *et al*. 1996, Sjögren *et al*. 1997, Trope *et al*. 1999, Ricucci *et al*. 2000, Weiger *et al*. 2000, Deutsch *et al*. 2001, Hoskinson *et al*. 2002, Murakami *et al*. 2002, Peters & Wesselink 2002) and less often general dental practitioners (Kerekes 1978, Barbakow *et al*. 1981a, Hession 1981, Cvek *et al*. 1982, Nelson 1982, Boggia 1983, Peak 1994, Peak *et al*. 2001) or postgraduate students (Cvek 1972, Adenubi & Rule 1976, Murphy *et al*. 1991, Chugal *et al*. 2001).

Root canal treatments performed by operators with lower levels of qualification and experience (students) may be more prone to procedural errors compared to experienced operators (Endodontic staff) and therefore have poorer anticipated outcomes; surprisingly Ingle (1965) found no significant difference by operative groups. Interestingly, other studies (Cheung 2002, Fouad & Burleson 2003, Field *et al*. 2004) have concurred with this finding. In contrast, Kerekes (1978) reported that the prevalence of faulty root fillings using gutta-percha points coated with Kloroperka N-O (N-O therapeutics, Oslo, Norway), was twice as high in the teeth treated by general dental practitioners compared to teeth treated by undergraduate students, resulting in lower success rates. However, case complexity and pre-operative periapical status were not controlled in these studies.

ii) Use of rubber dam isolation during treatment

The use of rubber dam in modern root canal treatment is so widely accepted that the absence of systematic data on its influence on root canal treatment outcome comes as a considerable surprise. None of the studies on primary treatment outcome had analysed the influence of rubber dam isolation. One study on secondary treatment (Van Nieuwenhuysen *et al*. 1994) had analysed the influence of rubber dam compared to cotton roll isolation and found significantly higher success rates with the former approach. Perhaps as a consequence, the principal justification for rubber dam use is driven through the medico-legal complications of root canal instruments inhalation by the patient, which it should prevent (European Society of Endodontology 2006).

iii) Type of instruments for canal preparation

The root canal system may be mechanically prepared to a requisite size and taper (Schilder 1974) using a variety of instruments of different cutting design, tapers, and materials of construction. Their efficacy is often tested in laboratory studies and the instruments may have well characterised properties (Hülsmann *et al*. 2005).

Treatments carried out by undergraduate students using nickel-titanium (NiTi) K-type files for canal preparation were found in a randomized controlled trial to be associated with less procedural errors and a significantly higher chance of success compared to those using stainless steel K-type files (Pettiette *et al*. 2001). The outcome of treatment carried out by full-time faculty members was not influenced by the type of NiTi rotary instruments (Lightspeed® [Lightspeed Inc., San Antonio, TX, USA], ProFile® .04 [Dentsply Maillefer, Ballaigues, Switzerland], ProFile® .04 & .06 [Dentsply Maillefer], or GT® [Dentsply Maillefer]) instruments used for canal preparation in a cohort study (Peters *et al*. 2004). The canals in the former two groups (Lightspeed®, ProFile®) were obturated using lateral compaction of gutta-percha but those in the last group (GT®) were obturated using the continuous-wave technique and was associated with a higher prevalence of extruded root filling material. Thus the true effect of instrument type could not be independently assessed.

iv) Apical extent of instrumentation

One of the ESE guidelines is that root canal cleaning must be extended to the apical constriction, or 0.5 – 2 mm from the radiographic apex, or to the cemento-dentinal junction. This guideline is broadly supported by the fact that outcome of primary root canal treatment is compromised by canal obstruction (Strindberg 1956, Engström *et al*. 1964, Cvek *et al*. 1982, Sjögren *et al*. 1990, Negishi *et al*. 2005). In contrast, Sjögren *et al*. (1990) and Gorni & Gagliani (2004) reported that the level of instrumentation had no significant influence on the outcome of secondary treatment on teeth with apical periodontitis. The contradictory findings on primary and secondary treatment by Sjögren *et al*. (1990) may simply be related to the insufficient sample size in their secondary treatment group. It could be speculated that the lack of mechanical negotiability of canals may be due to presence of denticles, separated instruments, acute branching or fine plexus of apical canals. Such *mechanical* obstruction may still allow irrigants to penetrate beyond the obstruction during treatment. Sjögren *et al*. (1990) did not distinguish between canals obliterated by denticles, tertiary dentine or obturation material.

During instrumentation, extension of the instruments beyond the canal terminus has been recognized as apical disturbance. Reports on the effect of apical disturbance by instrumentation have been contradictory (Harty *et al.* 1970, Adenubi & Rule 1976, Bergenholtz *et al*. 1979a, Nelson 1982). Harty *et al*. (1970) reported that apical disturbance resulted in a significantly higher success rate than absence of it. In contrast, Adenubi & Rule (1976) and Bergenholtz *et al*. (1979a) reported the contrary. Adenubi & Rule (1976) defined apical disturbance by including extrusion of sealer/filling, in addition to extrusion of instrument. In comparison, Bergenholtz *et al*. (1979a) pointed out that the majority of failures occurring among 'cleaned roots' (with apical disturbance) were complicated by overfilling during secondary treatment. Nelson (1982) found too few cases with apical disturbance for meaningful statistical analysis. In summary, instrumentation beyond the apical foramen, *without* foraminal enlargement, or transportation and concomitant filling material extrusion, may have a beneficial effect on treatment outcome.

v) Apical size of canal preparation

The debate on the optimal size of apical preparation remains topical in the absence of definitive evidence: the findings from relevant clinical and *in vitro* studies have been reviewed by Baugh & Wallace (2005). Only 3 clinical outcome studies have investigated the effect of apical size of canal preparation (Strindberg 1956, Kerekes & Tronstad 1979, Hoskinson *et al*. 2002). Although none of them had this as the principal focus of their study and none found a statistically significant influence, both Strindberg (1956) & Hoskinson *et al*. (2002) reported a trend of decreasing success rate with increase in the size of apical preparation. The reported trend was in contrast to the conclusion drawn by Baugh & Wallace (2005) based on a different outcome measure. They suggested a strong consensus that larger apical preparation sizes produced a greater reduction in remaining bacteria and dentinal debris.

vi) Taper of canal preparation

Alongside the issue of how much the canal terminus should be enlarged, sits the issue of the size and taper of the rest of the canal preparation. Again, there is a paucity of sufficient direct evidence for the influence of canal taper size on root canal treatment outcome. The ESE guidelines recommended only that canal preparation should be tapered from crown to apex without stipulating the degree of taper. Two studies have analysed the influence of canal preparation taper on primary and secondary root canal treatment outcome, although again, neither had this factor as a primary focus of their investigation (Smith *et al*. 1993, Hoskinson *et al*. 2002). Smith *et al*. (1993) using loose criteria for determination of success, found that a "flared" preparation (wide taper) resulted in a significantly higher success rate compared with a "conical" preparation (narrow taper); the exact degree of taper was not reported and the effects of confounders were not controlled. In contrast, Hoskinson *et al*. (2002) using strict criteria, did not find any significant difference in treatment outcome between narrow (.05) and wide (.10) canal tapers. It is known in the context of this study that the taper of preparation was correlated with both the concentration of sodium hypochlorite irrigant and root filling technique used. Therefore the true effect of taper could not be independently analysed.

vii) Technical errors during canal preparation

Procedural errors during root canal preparation may include canal blockage, ledge formation, straightening of canal curvature, apical zipping and transportation, tooth or root perforation at the pulp chamber or radicular level, and separation of instruments. Of these, the effects of ledge formation, apical zipping and transportation have not been specifically investigated. The effect of canal blockage has already been explored in the previous section 1.8.2.2 (vi). In this section, the effect of iatrogenic perforation and instrument separation are discussed.

Primary root canal treatments with iatrogenic perforations were found to result in significantly lower success rates (Cvek *et al*. 1982, Sjögren *et al*. 1990, Imura *et al*. 2007). This is in agreement with the reports on the presence of pre-existing perforation in secondary treatment discussed previously in section 1.8.2.1 (ix). The above studies did not analyse further the specific prognostic factors for teeth with perforation. A narrative review by Alhadainy (1994) concluded that time lapsed before defect repair, location and size of perforation, and adequacy of perforation seal were reported to be important factors on the basis of one case-series and the findings from *in vitro* and animal studies.

Instrument separation during primary or secondary root canal treatment was found to reduce the success rate significantly (Strindberg 1956, Imura *et al*. 2007). A case-control study has compared those teeth with retained separated instrument (cases) after primary or secondary treatment performed by endodontists and those without retained separated instrument (controls) (Spili *et al*. 2004). Amongst the teeth with periapical lesions, the success rate of teeth in the case group was 6% lower than the controls, but the difference was not statistically significant. The stage of canal debridement at which the instrument separation took place and the reasons for retaining the separated instrument may have implications in the outcome but were not discussed in their paper. The corono-apical location of a separated instrument and whether the instrument was successfully bypassed were found to have no effect on treatment outcome. The number of cases with instruments at the various levels in the canal was small and unevenly distributed; therefore the statistical power may have been insufficient. In their report, retained instruments were most prevalent in the apical third (77%). This was consistent with the finding, that overall, separated NiTi-instrument removal-rate was 53%; the favourable factors for removal were straight root canals, anterior teeth, localisation coronal to the canal curvature, fragments longer than 5 mm and hand NiTi K-files (Shen *et al.* 2004). Unfortunately, these findings were not correlated with periapical healing.

ix) Irrigant

Different types of chemical agents have been used as irrigants for root canal treatment, singly or in various combinations in clinical practice and in the studies reviewed. They have included solutions of: water, saline, local anaesthetic, sodium hypochlorite, iodine, chloramine, sulphuric acid, EDTA, hydrogen peroxide, organic acid, Savlon®, urea peroxide and a quaternary ammonium compound (Biosept®). Most of the studies had used sodium hypochlorite as an irrigant irrespective of primary or secondary root canal treatment. This is consistent with the ESE guidelines for canal irrigation which recommends a solution possessing disinfectant and tissue-dissolving properties. The recommendation is, however, based only on clinical microbiological and *ex vivo* microbiological data. There is an absence of studies systematically investigating the effect of the irrigant on the success rates of primary and secondary root canal treatment. One such clinical / microbiological study investigating the effect of irrigants found that using 0.5% sodium hypochlorite solution was associated with better healing than using a 5% solution, but the difference was not statistically significant (Cvek *et al.* 1976b).

x) Medicament

Most studies have not standardised the type of root canal medicament used in the inter-appointment period during root canal treatment, but the use of a number of medicaments has been reported. The list was consistent with that recommended in the ESE guidelines for a medicament with disinfectant properties and included: calcium hydroxide, phenolic compounds, iodine solutions, creosote, cresatin, formaldehyde-based compounds, corticosteroids, antibiotics, Grossman's solution, eugenol and a mixture of calcium hydroxide & chlorhexidine.

The influence of canal medicament on primary root canal treatment outcome has been investigated in a few studies but there is an absence of studies investigating the influence of this factor on secondary root canal treatment outcome (Adenubi & Rule 1976, Jokinen *et al.* 1978, Trope *et al.* 1999, Cheung 2002, Cheung & Chan 2003). The use of calcium hydroxide medicament resulted in better treatment outcome than teeth with no dressing (Trope *et al.* 1999, Cheung 2002) or one containing corticosteroid (Ledermix®) (Cheung 2002). The findings by Cheung (2002) were in total contrast to the finding that the medicament had no influence on treatment outcome in his later study (Cheung & Chan 2003). The discrepancy may be attributed to the difference in characteristics of the two studies: (1) the sample size was 2.4 times larger in the latter study; (2) treatments were performed in the 1980s in the latter and in the 1990s in the former study; and (3) phenolic compounds were used more often in the latter than in the former study. In contrast, roots treated with a medicament containing corticosteroid were found to have significantly better outcomes than those dressed with the same preparation without corticosteroid (Jokinen *et al.* 1978). However, the exact composition of the medicament was not given. When antibiotics were used as the canal medicament, the type (chloromycetin, neomycin) apparently had no influence on treatment outcome (Adenubi & Rule 1976).

Recently, the use of a mixture of calcium hydroxide and chlorhexidine has been tested based on the speculation that the mixture would be more effective against *E. faecalis* (Basrani *et al.* 2003, Gomes *et al.* 2003, Schäfer 2005). The rate of complete healing after secondary treatment using this medicament was 64% (Ercan *et al.* 2007) which is much lower than the previously reported average success rate of 82% (Hepworth & Friedman 1997).

xi) Root canal bacterial culture test results (positive or negative) prior to obturation

In the distant past, in various centres of endodontic excellence, completion of root canal treatment by root canal filling would only be triggered when a negative culture test result had confirmed the absence of bacteria (Buchbinder & Wald 1939, Morse & Yates 1941, Frostell 1963). However, this practice has fallen out of favour because of the perceived good prognosis of root canal treatment without microbiological sampling. Sampling procedures are considered lengthy and difficult as well as have low benefit/cost ratio (Molander *et al.* 1996a&b).

Reports from studies investigating the influence of bacterial culture results (prior to obturation) on primary and secondary treatment outcome have provided conflicting results. Half the studies found that canals with negative culture results were associated with significantly higher success rates than those with positive culture results (Buchbinder 1941, Frostell 1963, Engström *et al.* 1964, Engström & Lundberg 1965, Oliet & Sorin 1969, Sjögren *et al.* 1997, Sundqvist *et al.* 1998, Waltimo *et al.* 2005). In contrast, the others detected no significant difference (Seltzer *et al.* 1963, Bender *et al.* 1964, Storms 1969, Heling & Shapira 1978, Matsumoto *et al.* 1987, Peters & Wesselink 2002, Molander *et al.* 2007b). This could be attributable to the variations in: (1) field decontamination; (2) method of bacterial sampling from root canal; (3) bacterial detection; (4) their ability to detect residual apical infection; and (5) the lack of statistical power in some studies (Peters & Wesselink 2002, Molander *et al.* 2007b).

Interestingly, Bender *et al.* (1964) found that culture results had a significant influence on outcome of primary treatment when only the teeth associated with periapical lesions were considered. This was in agreement with Sundqvist *et al.* (1998) investigating the influence of this factor on secondary treatment.

xii) Root filling material and technique (single point gutta-percha, lateral condensation of gutta-percha, silver point, amalgam)

The inter-relationship between the root filling core material, sealer (for filling the gaps between the core material and canal surface) and technique for their placement, complicates the investigation of the effect of root filling material and technique on treatment outcome.

A number of root filling materials have been used in previous studies, including: gutta-percha, silver points, amalgam, Hydron® (poly-hydroxyethyl methacrylate), Alytit® (Syrian asphalt dissolved in benzene), iodoform paste, and Resilon® (bioactive glass in polycaprolactone polymers). The most commonly used materials were gutta-percha with various types of sealer (Buchbinder 1936, Morse & Yates 1941, Zeldow & Ingle 1963, Cvek et al. 1976, Heling & Shapira 1978, Vernieks & Messer 1978, Heling & Kischinovsky 1979, Barbakow 1980a&b, Hession 1981, Nelson 1982, Oliet 1983, Pekruhn 1986, Safavi *et al*. 1987, Shah 1988, Murphy *et al*. 1991, Friedman *et al*. 1995, Çalişken & Şen 1996, Gutknecht *et al*. 1996, Lilly *et al*. 1998, Trope *et al*. 1999, Ricucci *et al*. 2000, Weiger *et al*. 2000, Deutsch *et al*. 2001, Heling *et al*. 2001, Benenati & Khajotia 2002, Hoskinson *et al*. 2002, Peters & Wesselink 2002) or gutta-percha softened in chloroform (chloropercha) (Auerbach 1938, Grahnén & Hansson 1961, Forstell 1963, Engström & Lundberg 1965, Jokinen *et al*. 1978, Kerekes 1978, Soltanoff 1978, Kerekes & Tronstad 1979, Cvek *et al*. 1982, Morse *et al*. 1983a,b&c, Byström *et al*. 1987, Halse & Molven 1987, Akerblom & Hasselgren 1988, Molven & Halse 1988, Sjögren *et al*. 1990, Cvek 1992, Ørstavik 1996, Sjögren *et al*. 1997). One study used iodoform paste for obturation of all their cases (Castagnola & Orlay 1952).

The list of sealers used in previous studies included: Zinc oxide eugenol-based (Bioseal®, Grossman® cement, Procosol®, Roth's root canal sealer®), resin-based (AH26®, Epiphany®), glass ionomer-based (Ketac Endo®), calcium hydroxide-based (CRCS®, Sealapex®), silicone-based (Roeko seal Automix®, Roeko, Langenau, Germany) and paraformaldehyde-based (Endomethasone®) sealer. Zinc oxide eugenol-based and resin-based (AH26®) sealers were the most frequently used.

Most of the studies investigating the effects of root filling materials and/or techniques on primary and secondary treatment outcome, did not find any significant influence of this factor (Strindberg 1956, Seltzer *et al*. 1963, Bender *et al*. 1964, Heling & Tamshe 1970 & 1971, Adenubi & Rule 1976, Swartz *et al*. 1983, Teo *et al*. 1986, Reid *et al*. 1992, Peak 1994, Friedman *et al*. 1995). There were, however, some exceptions; Reid *et al*. (1992) found that gutta-percha root fillings were associated with failure significantly less often than Hydron® root fillings. Smith *et al*. (1993) reported that root canals filled with apical amalgam followed by lateral compaction of gutta-percha coronally were associated with significantly higher success rates than those filled with apical amalgam only. However, they did not consider potential confounders, such as size of canal preparation, in their analysis.

When comparing various techniques for placing gutta-percha, cold lateral compaction was normally used as the control technique in many previous studies. Van Nieuwenhuysen *et al*. (1994) found that the use of a single-cone technique was associated with a lower success rate. The use of warm vertical compaction technique was found to achieve higher healing rates for primary treatment in the observational "Toronto study" (Friedman *et al*. 2003, Farzaneh *et al*. 2004a, de Chevigny *et al*. 2008a). This finding was corroborated by Aqrabawi (2006) who did not stratify his analyses by primary or secondary treatments. Curiously, the finding did not hold true for secondary treatment in the "Toronto study" (Farzaneh *et al*. 2004b, de Chevigny *et al*. 2008b). Whilst the periapical status was controlled, the potential confounding effects of apical extent of canal preparation and root fillings were not accounted for in any of the "Toronto studies". The use of thermoplasticised gutta-percha with a solid core (Thermafil®) was found to be associated with a significantly higher success rate in two studies (Zheng *et al*. 2004, Bing *et al*. 2005) but not a third (Chu *et al*. 2005). In summary, there is a lack of firm evidence to support the view that putatively improved filling of the irregular canal space using thermoplasticised gutta-percha technique should have a beneficial influence on treatment outcome. This observation could be supported by the results of a meta-analysis in a recent systematic review (Peng *et al*. 2007). The validity of pooling outcome data by different thermoplasticised gutta-percha techniques (Thermafil®, warm vertical compaction or injectable gutta-percha) in their analyses has been challenged (Spångberg 2007). The variation in thermoplasticising technique, together with other clinical heterogeneities, such as variations in study type, the duration of follow-up, the criteria for success and apical extent of root fillings may lead to substantial statistical heterogeneity which was not considered in their analyses.

When comparing various types of sealers, zinc oxide eugenol-based sealers have been frequently used as the control material (Adenubi & Rule 1976, Nelson 1982, Ørstavik *et al*. 1987, Eriksen *et al*. 1988b, Waltimo *et al*. 2001, Huumonen *et al*. 2003). Nelson (1982) reported that a number of test sealers (KRI paste®, N2®, Endomethasone®, Spad®) were associated with significantly lower success rates compared to the controls. Using PAI scoring and RIDIT analysis, Ørstavik *et al*. (1987) and Eriksen *et al*. (1988b) reported that teeth with pre-operative vital pulps filled using a resin-based sealer (AH26®) achieved similar average RIDITs, but Kloroperka N-Ø® achieved lower RIDITs at follow-up when compared with the use of control sealer (ProcoSol®). Although PAI scoring/RIDIT analysis was effective in detecting the difference, the proportion of successful treatment by each test group was not apparent, rendering interpretation and comparison of the results with other study difficult. Interestingly, the use of calcium hydroxide-based sealer (CRCS®) achieved more rapid healing but similar long-term outcome when compared with the use of control sealer. No significant difference in treatment outcome was found between the use of zinc oxide eugenol-based sealers with or without accelerator (Adenubi & Rule 1976) and between zinc oxide eugenol-based and silicone-based sealers (Huumonen *et al*. 2003).

Recently, an endodontic root filling material (Resilon®, Pentron Clinical Technologies, Wallingford, CT, USA) made of polycaprolactone polymer and various fillers (bioactive glass, bismuth oxychloride, barium sulphate) used with a corresponding dual-cure dental resin composite sealer (Epiphany Root Canal Sealant, Pentron clinical Technologies) was developed as an alternative to gutta-percha, citing its superior sealing ability (Sagsen *et al*. 2006, Tunga & Bodrumlu 2006, Stratton *et al*. 2006). Conner *et al*. (2007) reported much higher success rates of treatment using this filling material for teeth *without* pre-operative periapical lesion (90%) compared with teeth *with* pre-operative periapical lesion (50%). The latter was at the lower end of the range of success rates (46% – 91%) for teeth with periapical lesions (Friedman 2002). When the success rates of teeth filled with Resilon® together with resin sealer or gutta-percha with eugenol-based sealer were compared, no significant difference was found (Cotton *et al*. 2008).

On the basis of the above findings, it may be concluded that there is no justification at present to replace the use of cold lateral compaction of gutta-percha cones and zinc oxide-eugenol sealer with any other root filling material or technique. Conversely, it may be concluded that the new materials, so far show equivalent periapical healing potential and may reasonably be adopted.

xiii) Apical extent of root filling

Of the many intra-operative factors, this has been the most frequently and thoroughly investigated, presumably because it offers a readily measurable outcome, retrospectively. In these previous studies, the apical extents of root fillings have been classified into three categories for statistical analyses: > 2mm short of radiographic apex (short), 0–2 mm within the radiographic apex (flush) and extended beyond the radiographic apex (long). The strategy for this stratification has not been specifically justified in previous studies but it is possible to offer a rational explanation based on average length measurement of root end anatomy. Some studies defined acceptable apical extents of root fillings as those ending between 0–1mm within the radiographic apex (flush) (Harty *et al*. 1970, Kerekes *et al*. 1978, Kerekes & Tronstad 1979). Under-extended root fillings have been further sub-classified into 4 groups: under-extended by 1.1–2.0 mm, 0.5–1.0 mm, 0–0.4 mm (Matsumoto *et al*. 1987). Friedman's group have instead dichotomized this factor into adequate (flush) and inadequate (short or long) categories (Friedman *et al*. 1995, Farzaneh *et al*. 2004b, de Chevigny *et al*. 2008b).

Without stratifying the analysis by the presence of periapical lesion, the apical extent of root filling was found to have a significant influence on the success rates of primary and secondary treatment. Flush root fillings were associated with higher success rates than short root fillings (Strindberg 1956, Storms 1969, Harty *et al*. 1970, Adenubi & Rule 1976, Nelson 1982, Morse *et al*. 1983 a,b&c, Sjögren *et al*. 1990, Ørstavik & Hörstad-Bindslev 1993, Smith *et al*. 1993) or long root fillings (Strindberg 1956, Seltzer *et al*. 1963, Bender *et al*. 1964, Engström *et al*. 1964, Harty *et al*. 1970, Adenubi & Rule 1976, Jokinen *et al*. 1978, Nelson 1982, Swartz *et al*. 1983, Klevant & Eggink 1983, Oliet 1983, Sjögren *et al*. 1990, Ørstavik & Hörstad-Bindslev 1993, Smith *et al*. 1993, Doyles *et al*. 2007). Short root fillings in turn had significantly higher success rates than long root fillings (Grahnén & Hansson 1961, Seltzer *et al*. 1963, Bender *et al*. 1964, Engström *et al*. 1964, Adenubi & Rule 1976, Jokinen *et al*. 1978, Bergenholtz *et al*. 1979a&b, Nelson 1982, Klevant & Eggink 1983, Oliet 1983, Swartz *et al*. 1983, Teo *et al*. 1986, Matsumoto *et al*. 1987, Ørstavik & Hörstad-Bindslev 1993). These observations are consistent with results from previous meta-analyses (Kojima *et al*. 2004, Schaeffer *et al*. 2005). Although Schaeffer *et al*. (2005) found the same trend, it was not statistically significant. This may be attributable to the small number of studies (n=4) included in their analyses and the designation of the definition for flush root filling as 0–1mm within the radiographic apex. With the small proportion of short or long root fillings amongst their samples, some studies also found the similar trend that long root fillings were associated with the lowest success rates, although the difference was not statistically significant (Soltanoff 1978, Halse & Molven 1987, Byström *et al.* 1987, Peak 1994, Sjögren *et al*. 1997, Hoskinson *et al*. 2002, Cheung & Chan 2003, Khedmat *et al*. 2004).

The interaction between the effects of pre-operative periapical lesion and apical extent of root filling has been investigated in a number of studies (Bender *et al*. 1964, Halse & Molven 1987, Sjögren *et al*. 1990, Smith *et al*. 1993, Farzaneh *et al*. 2004a&b, de Chevigny *et al*. 2008a&b). For teeth with vital pulps and no pre-operative periapical lesion, the apical extent of root fillings had no impact on the treatment outcome (Sjögren *et al*. 1990, Smith *et al*. 1993, Gesi *et al*. 2006). Teeth with a pre-operative periapical lesion and flush root fillings had significantly higher success rates (Bender *et al*. 1964, Sjögren *et al*. 1990, Smith *et al*. 1993) than teeth with short or long root fillings. Bender *et al*. (1964) found that teeth with short root fillings had higher success rates than those with long root fillings. With the smaller proportion of teeth with short (11%) or long (27%) root fillings in their study, an opposite but insignificant finding was reported by Sjögren *et al*. (1990). In stark contrast, Heling *et al*. (2001) using "tooth" as the unit of assessment and loose criteria for success, found a reverse trend with long root fillings associated with better outcome than short or well-performed root fillings. A possible explanation is that the latter two categories were associated with larger pre-operative periapical lesions.

There were conflicting findings on the effect of apical extent of root fillings reported from the different phases of the "Toronto study" on the outcome of secondary root canal treatment on teeth with periapical lesions. When the apical extent of root fillings were categorized into short, flush and long, they were found to have no significant effect on treatment outcome (Farzaneh *et al*. 2004b). A significant association was, however found after combining long and short root-fillings into one category under the label of "inadequate" root filling (Farzaneh *et al*. 2004b). The odds ratio for adequate root fillings (OR = 6.8; 95% CI: 1.2, 38.6) based on the data from phases 1&2 of their study (Farzaneh *et al*. 2004b) had very wide confidence interval, indicating imprecision in the estimation. In contrast, when data from phases 1–2 (Farzaneh *et al*. 2004b) and phases 3–4 (de Chevigny *et al*. 2008b) of the Toronto study were pooled for analyses, this relationship no longer held true. This illustrates spurious results obtained from analyses using small sample sizes. The use of “tooth” as unit of assessment may also render analyses of this root-level variable problematic.

Curiously, whilst Sjögren *et al*. (1990) found the extent of root filling to have significant influence on outcome of primary treatment on teeth with periapical lesions, they could not find such a relationship for secondary treatment. The authors stressed that all cases with short root fillings and pre-operative periapical lesions were classified amongst those that could not be instrumented to their full length. Closer inspection of their data revealed that secondary treatment teeth with pre-operative periapical lesions and long root fillings (50% of 26 roots) were associated with 15–17% lower success rates compared with those teeth that had flush (0–2 mm short of radiographic apex) (67% of 51 roots) or short (≤ 2mm short of radiographic apex) (65% of 17 roots) root fillings. The reported lack of statistical significance may be due to insufficient sample size. It was also noted that the secondary treatment cases with flush root fillings (67%) were associated with a much lower (27%) success rate than their primary treatment (94%) counterparts. It could be speculated that the canal termini in many of the secondary treatment cases may have been transported due to over-instrumentation and, therefore located further away from the radiographic apex compared to the previously untreated canals. Perhaps, given this complication, a direct comparison between flush root fillings in primary and secondary treatment cases may require different measures, possibly involving the use of electronic apex locators.

The fate of extruded root fillings has been studied radiographically by Halse & Molven (1987). At 10–17 years after treatment, 79% of the extruded Kloroperka N-Ö had disappeared, 18% had reduced in amount and 3% remained unchanged. Small extrusions (2mm or less) (90%) disappeared more readily than gross extrusions (>2mm) (45%). They therefore concluded that apical overfilling *per se* had little influence on the long-term outcome of healing except for teeth with gross extrusion. However, the effect of extended root filling material on the *rate of healing* has not been reported in the literature.

xiv) Quality of root filling

An unsatisfactory root filling has been defined as “inadequate seal”, “poor apical seal” or “radiographic presence of voids”; whilst some studies also took into consideration the apical extent of the root fillings (Storms 1969, Van Nieuwenhuysen *et al.* 1994). Satisfactory root fillings were found to be associated with significantly higher success rates than unsatisfactory root fillings for both primary and secondary treatment (Harty *et al.* 1970, Adenubi & Rule 1976, Heling & Kischinovsky 1979, Nelson 1982, Teo *et al*. 1986, Halse & Molven 1987, Van Nieuwenhuysen *et al*. 1994, Iqbal *et al*. 2003, Farzaneh *et al*. 2004b). Cheung (2002) found that voids in root fillings at the middle or apical thirds had significantly worse outcome than those with voids in the coronal third or those without voids; this was in total contrast to their later findings (Cheung & Chan 2003). Other studies with only a small proportion (5% – 10%) of cases with unsatisfactory root fillings, also reported that the quality of root fillings had no significant influence on primary treatment outcome (Sjögren *et al*. 1990, Heling *et al*. 2001).

xv) Apical disturbance by extruded medicament or sealer

Extrusion of calcium hydroxide paste dressing in teeth with large periapical lesions was found to have no significant influence on the outcome of treatment (Çalişken & Şen 1996).

Signs for “sealer puffs” extruding through the main and lateral/accessory canals have been perceived as “good practice” by some endodontists, as it has been taken as a surrogate measure of root canal system cleanliness (Nguyen 1994). The reports on the effects of sealer extrusion into periapical tissues have been contradictory. Friedman *et al*. (1995) found extrusion of Ketac-Endo® sealer reduced success rates significantly, in contrast to Sari & Durutűrk (2007) who reported that extrusion of AH Plus® (Dentsply/DeTrey, Konstanz, Germany) sealer did not prevent but only delayed periapical healing. The discrepancy may be attributed to the difference in the duration of follow-up after treatment: 6–18 months by Friedman *et al*. (1995) compared with 48 months by Sari & Durutűrk (2007).

Extruded glass ionomer-based (Friedman *et al*. 1995), zinc oxide eugenol-based (Huumonen *et al*. 2003), silicone-based (Huumonen *et al*. 2003) sealers or Endomethasone® (Boggia 1983) were found not to be absorbed by periapical tissues after one year. Traces of calcium hydroxide-based sealer (Sealapex®) could still be detected even after three years (Sari & Okte 2008). In the latter study, treatments were carried out on primary molar teeth and the canals were obturated with Sealapex® without gutta-percha. With the longer duration of follow-up, complete resorption of the extruded zinc-oxide eugenol-based sealers (Procosol®, Roth Elite®) (Augsberger & Peters 1990) and resin-based sealer (AH Plus, Dentsply/DeTrey, Konstanz, Germany) (Sari & Durutűrk 2007) occurred in 69% and 45%, of the cases after 4 and 5 years, respectively.

xvi) Acute exacerbation during treatment

The aetiological factors for inter-appointment “flare-up” or pain have not been precisely determined and several hypothetical mechanisms such as chemical, mechanical or microbial injury to the periradicular tissues and psychological influences have been suggested as possible causes of post-preparation pain (Seltzer & Naidorf 1985a&b). Although this factor has not been specifically studied, acute “flare-ups” during treatment were found to have no significant effect on outcome (Kerekes & Tronstad 1979, Byström *et al*. 1987, Sjögren *et al*. 1990). However, none of these studies presented summary data by this factor for critical appraisal. These unexpected findings warrant more systematic evaluation.

xvii) Number of treatment visits

Most previous studies have carried out all treatments over multiple visits, whilst in some studies all treatment was completed in a single visit (Boggia 1983, Ashkenaz 1984, Pekruhn 1986, Jurcak et *al*. 1993, Sjögren *et al*. 1997, Field *et al*. 2004). All studies have collectively found no significant difference in success rates between single- and multiple-visit treatments (Soltanoff 1978, Oliet 1983, Van Nieuwenhuysen *et al*. 1994, Trope *et al*. 1999, Weiger *et al*. 2000, Deutsch *et al*. 2001, Cheung 2002, Peters & Wesselink 2002, Cheung & Chan 2003, Farzaneh *et al*. 2004a&b, Gesi *et al*. 2006, Doyles *et al*. 2007, Molander *et al*. 2007b, Penesis *et al*. 2008). This finding has been corroborated by two systematic reviews (Sathorn *et al*. 2005b, Figini *et al*. 2007). The former meta-analysis only included three randomized controlled trials and only those cases with pre-operative periapical lesions and treated with calcium hydroxide were included in the multiple-visit treatment dataset (Trope *et al*. 1999, Weiger *et al*. 2000, Peters & Wesselink 2002). They, in fact, found single-visit treatment to be slightly more effective (6.3%; OR = 1.35, 95%CI 0.63, 2.88) than multiple-visit treatment but emphasised the lack of power in the three studies as well as in the pooled data. A sample size of 433 – 622 was deemed necessary for a difference in 10% success rate to be detected in such a trial. It would be interesting to repeat the meta-analysis by including three other randomized controlled trials published after their review (Gesi *et al*. 2006, Molander *et al*. 2007b, Penesis *et al*. 2008).

One of the important issues related to the design of randomized controlled trials to investigate this clinical question is the strategy for handling those cases in the one-visit group that could not be completed within a single visit due to technical or biological problems. The earlier trials did not address this issue. Gesi *et al*. (2006) mentioned that if there was insufficient time to complete the treatment in the assigned session; those cases would be completed within one week but made no mention about the impact of this strategy on analysis. Molander *et al*. (2007b) only included patients with asymptomatic teeth. Penesis *et al*. (2008) excluded such cases from the final analysis. From a research design perspective, cases designated for single-visit treatment as a random allocation, should be completed as intended; if the case fails then retreatment should be provided. Cases requiring subsequent re-treatment should therefore be designated as failures. There is therefore a conflict between adherence to research design protocol and adherence to ethical protocol. A further factor often not considered is that the skill and experience of clinicians may confound the results. This factor may be controlled by recruiting a single operator but the problem is generalisation of the results. It is therefore more appropriate to recruit a large group of operators with mixed skills and background and to adopt a robust randomization strategy. The influence of skill and background may be studied to give a better indicator of generalisation of results.

For multiple-visit secondary treatment, Van Nieuwenhuysen *et al*. (1994) have specifically reported that the outcome was significantly improved by completing both the canal preparation and disinfection within the first visit.

1.9.2.3 Post-operative (root canal treatment) factors

i) Quality and type of coronal restoration after RCT

The majority of root treated teeth will be subsequently restored; this is usually the primary intent from an aesthetic, functional and biological rationale. The goal is to prevent coronal leakage and protect remaining tooth tissue from further damage (Gulabivala 2004b). Depending upon the primary aesthetic or functional needs and the patient expectations, the tooth may be restored with a plastic filling material (amalgam, composite), cast partial restoration, or cast full restoration (with or without porcelain). The quality and type of restorations have been stratified differently in previous studies; for example, satisfactory vs unsatisfactory, restored vs unrestored, permanent vs temporary, intra- vs extra-coronal or presence vs absence of post.

Teeth with coronal restorations of satisfactory quality were found to be associated with higher success rates by two studies (Swartz *et al*. 1983, Iqbal *et al*. 2003) but not by the other two (Teo *et al*. 1986, Khedmat *et al*. 2004). None of these studies had given the criteria used to determine restoration quality, which may explain the discrepancy in their findings. Hoskinson *et al*. (2002) defined satisfactory restorations as those with no evidence of discrepancy, discolouration or recurrent caries at the restoration margin, with absence of a history of de-cementation. They could not however, analyze the effect of this factor because there was insufficient number of cases with unsatisfactory restorations (19%) in their sample.

Those teeth without restoration and the gutta-percha filling exposed to the oral cavity were found to be significantly associated with lower success rates than those with a restoration (Friedman *et al*. 1995, Imura *et al*. 2007). Although Ricucci *et al*. (2000) found a difference (3-fold), it was not statistically significant, again probably due to the small sample size. Surprisingly, they suggested that the problem of coronal leakage may not be of such great clinical importance simply on the basis of their (imprecise) findings.

When comparing temporary and permanent restorations, temporary restorations were associated with lower success rates in some studies (Heling & Kischinovsky 1979, Allen *et al*. 1989, Fouad & Burleson 2003, Farzaneh *et al*. 2004b), but not in others (Safavi *et al*. 1987, Friedman *et al*. 1995, Friedman *et al*. 2003, Farzaneh *et al*. 2004a, Chugal *et al*. 2007, de Chevigny *et al*. 2008a). Chugal *et al*. (2007) highlighted the importance of adjusting the results of such an analysis for pre-operative periapical status of teeth as there may be specific biological reasons for delaying the placement of a permanent restoration after treatment, such as in case of large periapical lesions.

The various types of permanent restorations had no significant effect on treatment outcome: definitive plastic vs cast restoration (Friedman *et al.* 1995); amalgam vs composite vs post-amalgam vs crown vs post-crown (Heling *et al.* 2001); simple coronal vs cuspal coverage (Cheung 2002); amalgam vs composite vs glass ionomer (Zmener *et al.* 2007). Sjögren *et al*. (1990) reported that teeth with a crown were associated with a significantly lower success rate for primary treatment but had no association with the outcome of secondary treatment. In contrast to the above studies, some found that root treated teeth with prosthetic reconstruction (Heling & Tamshe 1970 & 1971, Heling & Shapira 1978), or extra-coronal restorations (Cheung & Chan 2003, Chu *et al.* 2005) were associated with significantly better outcome than their contrary counterpart. In addition, teeth restored with post-retained amalgam were associated with longer healthy state (including tooth survival) than teeth restored with no post or cast-post (Cheung & Chan 2003, Doyles *et al.* 2007). For those teeth restored with post-retained prosthesis, the success rates were found to be reduced by the increase in the width of the gap between the post and gutta-percha root filling (Moshonov *et al.* 2005).

In summary, the above findings supported the ESE guidelines that an adequate restoration should be placed after root canal treatment to prevent subsequent bacterial recontamination and tooth fracturing.

ii) Use as abutment for prosthesis and occlusal contacts

The stress on teeth is a function of occlusal loading as well as the manner in which teeth are loaded i.e., single unit, bridge abutment or denture abutment. It may be expected that bridge and denture abutments may be placed under unfavourable loads, as may terminal teeth (Matsumoto & Goto 1970, Shillingburg *et al.* 1981). Such teeth may therefore be expected to have lower success rates.

Teeth with occlusal contacts were associated with significantly lower success rates after primary root canal treatment (Iqbal *et al.* 2003). The expectation that teeth functioning as bridge (Sjögren *et al.* 1990) or denture (Matsumoto *et al.* 1987) abutments would have lower success rates than teeth restored as individual units was confirmed for primary treatment in the respective studies. Contrary to expectation, Storms (1969) found no such significant difference but their analyses were not stratified for non-surgical and surgical treatments. Curiously, Sjögren *et al*. (1990) did not find that teeth used as abutments had a significantly different outcome in secondary treatment.

1.9.3 Overview of prognostic factors for survival of teeth after primary or secondary root canal treatment

Compared with studies on periapical healing, far fewer studies have investigated the survival of teeth after root canal treatment. Most were retrospective cohort studies (Lazarski *et al.* 2001, Aquilino & Caplan 2002, Dammaschke *et al*. 2003, Alley *et al*. 2004, Salehrabi & Rotstein 2004, Stoll *et al*. 2005, Chen *et al*. 2007, Salvi *et al*. 2007). They were mostly designed to answer different clinical questions, some related to survival of the restoration and other of the restoration and tooth. The sample size ranged widely from 50 [Tan *et al.* 2006] to 1,462,936 [Salehrabi & Rotstein 2004] teeth. The former was a prospective study investigating the survival of teeth with cracks and root canal treatment, whilst the latter was a large epidemiological retrospective study based on insurance company data. The insurance company had a profile of insuring approximately 14 million individuals in 50 states across the USA. Although a retrospective epidemiological study allows inclusion of a very large cohort, the accuracy and extent of recorded details for investigation of prognostic factors is usually compromised [Lazarski *et al.* 2001, Salehrabi & Rotstein 2004]. The post-endodontic restorations were mostly provided in the same department in which the study was carried out [Caplan & Weintraub 1997, Aquilino & Caplan 2002, Caplan *et al.* 2002, Dammaschke *et al.* 2003, Alley *et al.* 2003, Lynch *et al.* 2004, Nagasiri & Chitmongkolsuk 2005, Tan *et al.* 2006, Lumley *et al.* 2008]. The implication of this observation is that they may potentially report a higher chance of tooth survival than those teeth with the final restorations provided by generalists, given that dentist's experience and qualification were significant prognostic factors for restoration survival [Lucarotti *et al.* 2005, Burke & Lucarotti 2008].

1.9.3.1 Tooth survival rates after root canal treatment

The 10-year tooth-survival probabilities ranged from 75% [Caplan *et al.* 2002] to 89% (74% cumulative survival rate) [Stoll *et al.* 2005, Lumley *et al.* 2008]. The range of 5-year survival probabilities was wider: 36% [Nagasiri & Chitmongkolsuk 2005] to 93% [Alley *et al.* 2004, Chen *et al.* 2007]. The former study only included molar teeth not restored with cusp-covered restorations (regardless of remaining tooth tissue) whilst, 85% of the teeth were crowned after treatment in the latter study.

Extraction was the most frequent treatment instituted when primary root canal treatment was deemed to have failed [Salehrabi & Rotstein 2004, Chen *et al.* 2007, Lumley *et al.* 2008]. The former study found most extractions took place within three years after root canal treatment but extractions occurred more evenly over the 5- or 10-year period in the latter two studies. The mean duration after treatment for untoward events (extraction or further endodontic treatment) to occur was 20 months [Lazarski *et al.* 2001]. Of the many reasons for extraction of root treated teeth, the most common was "large carious lesion" or "unrestorable tooth", followed by tooth fracture, periodontal disease and lastly endodontically related diseases [Chen *et al.* 2008].

Of those teeth surviving following treatment, only a small proportion had undergone further non-surgical (0.31% – 2.47%) or surgical re-treatment (0.45% – 1.41%) [Lazarski *et al.* 2001, Salehrabi & Rotstein 2004, Chen *et al.* 2007]. Surgical re-treatments were carried out more frequently on anterior teeth as compared with premolar or molar teeth [Lazarski *et al.* 2001, Salehrabi & Rotstein 2004].

1.9.3.2 Investigation of prognostic factors for tooth survival

The prognostic factors investigated could be classified into: general patient factors; pre-operative tooth factors; intra-operative factors; and post-operative restorative factors. Some studies also considered competing failure outcomes to tooth extraction, such as teeth undergoing surgical or non-surgical re-treatment (Stoll *et al*. 2005, Lumley *et al*. 2008, Tickle *et al*. 2008). Therefore the prognostic factors identified by these studies may be different from those identified by others.

1.9.3.3 General and pre-operative prognostic factors

i) Qualification of operators

One retrospective study was specifically designed to investigate this factor and found that teeth with treatment carried out by specialist Endodontists (98.1%) were associated with a higher probability of tooth survival over 5 years than those treated by generalists (89.7%) (Alley *et al*. 2004). This was contrary to the findings of others (Caplan & Weintraub 1997, Larzarski *et al*. 2001, Stoll *et al*. 2005). The sample size in Caplan & Weintraub's study (1997) was small. The study by Larzarski *et al*. (2001) was a large retrospective study with 44,613 cases covered by an insurance company. They, however, found that those cases undergoing additional surgical endodontic treatment by non-endodontists was associated with a significantly higher chance of tooth extraction. Stoll *et al*. (2005) found no difference in survival of root filling (subsequent replacement of root filling, periradicular surgery and tooth extraction were considered as failure) completed by qualified dentists or dental students.

Amongst general dental practitioners within the England and Wales National Health Service system, their employment status (assistant, principal, vocational), age, and country of qualification did not influence the survival of root treated teeth (Lumley *et al*. 2008).

ii) Sex, age, medical status and ethnic origin of patient

The influence of several patient factors has been investigated. They include gender, age, ethnic origin, medical condition, dental treatment history, and dental treatment fee paying status.

None of the previous studies have found any significant association between survival of teeth after root canal treatment and sex of the patient (Caplan & Weintraub 1997, Lazarski *et al*. 2001, Caplan *et al*. 2002, Dammaschke *et al*. 2003, Nagasiri & Chitmongkolsuk 2005, Tan *et al*. 2006).

After root canal treatment, the incidence of subsequent extraction of the teeth for both genders was found to be increased by 1% to 2% for each decade of the patient's age, reaching a plateau after age 60 (Lazarski *et al*. 2001). A similar trend was reported by Lumley *et al*. (2008) who compared survival of teeth to extraction or further treatment by each decade of the patient's age. In concurrence with this finding, Caplan

& Weintraub (1997) dichotomized patients' age at 50 years and found older age was significantly associated with more loss of teeth undergoing root canal treatment. Using much smaller sample sizes, some studies found no statistically significance difference in tooth survival by age (Aquilino & Caplan 2002, Dammaschke *et al.* 2003, Nagasiri & Chitmongkolsuk 2005). The continuous age variable has been categorized differently into 3 (Aquilino & Caplan 2002, Nagasiri & Chitmongkolsuk 2005) to 4 (Dammaschke *et al.* 2003) bands by the above studies, rendering direct comparison of results from previous studies impossible.

Only one study in Singapore has investigated the influence of the ethnic origin (Chinese, Indian, others) of patients on survival of root filled cracked teeth; they found no significant relationship (Tan *et al.* 2006). However, the number of patients of Indian (5/49) and other (3/49) origins were too small for valid statistical analyses.

Amongst many medical conditions afflicting such patient groups, only diabetes and hypertension have been investigated and were found to be associated with a higher chance of loss of root treated teeth (Mindiola *et al.* 2006). Using a much smaller sample size, Caplan *et al*. (2002) found no difference in tooth survival after primary treatment between patients requiring medication for hypertension/heart disease or not.

Survival of root treated teeth was also poorer amongst patients who had a high incidence of dental treatment (Lumley *et al.* 2008). On the basis of this finding, the authors questioned whether root canal treatment can be justified in this group of patients, as they may have poor oral hygiene, high caries rate, poor motivation, and pre-operatively un-restorable crown of the root treated teeth.

iii) Location and type of tooth

Second molar teeth (Aquilino & Caplan 2002, Caplan *et al.* 2002), molar teeth (Caplan *et al.* 2005) or posterior teeth (Lazarski *et al.* 2001) were associated with a lower chance of survival after root canal treatment. This was in contrast to the findings by others (Caplan & Weintraub 1997, Dammaschke *et al.* 2003, Tan *et al.* 2006). They had included relatively small sample sizes, failed to dichotomize molar teeth by first or second molars, and did not find any significant influence by tooth type. When comparing the teeth in the maxillary and mandibular arches, all previous studies found no difference in the probabilities of tooth survival (Dammaschke *et al.* 2003, Nagasiri & Chitmongkolsuk 2005, Tan *et al.* 2006, Lumley *et al.* 2008).

iv) Remaining tooth structure and presence of crack(s)

Root canal treatment should only be carried out if the restorability of the tooth has been ascertained (Gulabivala 2004b). At present, no criteria that have been calibrated with long-term outcome are available to guide clinicians in assessing the degree of tooth restorability. Only one retrospective study has reported that the amount of remaining tooth structure was positively associated with survival of molar teeth without crown coverage after root canal treatment (Nagasiri & Chitmongkolsuk 2005). The remaining structure was categorized into three types: Type I – maximum remaining structure approximating a class I preparation with at least 2 mm of surrounding wall thickness; type II – moderate remaining structure approximately a class II cavity preparation with no less than 2 walls with at least 2mm thickness; and type III – minimum remaining structure with less than 2 walls with at least 2 mm thickness. The median survival time for type II (4 years) and III (3 years) teeth was half of the median survival time (>7.9 year) for type I teeth. Given the large difference in median survival time between type I and II teeth but small difference between type II and III teeth, there is a need to devise a more detailed sub-classification for type II teeth (such as loss of one or both marginal ridges) for better prediction of tooth survival at the outset of root canal treatment. Alternatively, the clinical inference is that all the type II and III teeth should be protected with cast restoration after root canal treatment.

The survival of teeth with cracks prior to primary treatment has been specifically investigated in one prospective study [(Tan *et al.* 2006)]. A large proportion (85.5%) of these teeth survived after 2 years post-operatively. Tooth survival was influenced by the number of pre-operative cracks but not their location and extension. The teeth were either restored with a crown or an amalgam core with an orthodontic band for protection. A longer follow-up study is warranted for teeth with this problem as they pose a dilemma in decision-making on treatment options.

v) Pulpal and periapical status

Amongst the pre-operative conditions of teeth, the effects of pulpal and periapical status, pain experience, and previous root canal treatment on tooth survival have been investigated. Teeth with vital pulp [(Stoll *et al.* 2005)], absence of periapical lesion [(Dammaschke *et al.* 2003, Stoll *et al.* 2005)] or absence of pain [(Stoll *et al.* 2005)] prior to root canal treatment were associated with significantly longer survival times or higher chance of survival than their counterparts after 10 years post-operatively. Aquilino & Caplan (2002) found a 7% difference in the survival rate of teeth with or without pre-operative periapical lesion, although the difference was not significant; a finding which could be attributed to the small proportion (26%) of teeth with pre-operative lesions. In contrast to Stoll *et al.* (2005), Caplan & Weintraub (1997) found no difference in the prevalence of pre-operative pain between extracted teeth and surviving teeth in a case-control study. The discrepancy may be attributed to the fact that the former study had a larger sample size and defined failure event as teeth undergoing subsequent non-surgical or surgical treatments in addition to tooth extraction [(Stoll *et al.* 2005)].

Given that the survival of teeth with previous treatment might be worse as they have already failed or were destined to fail, Caplan *et al.* (2002) limited their analysis to teeth undergoing primary root canal treatment. Contrary to the above speculation, Stoll *et al.* (2005) reported no significant difference in the survival time of teeth following primary or secondary treatment. They did however; point out that only 13% of the teeth had undergone secondary treatment.

1.9.3.4 Intra-operative prognostic factors

Out of all the potential intra-operative factors, only the effects of apical extent and quality of root filling on tooth survival have been investigated.

i) Apical extent of root filling

Similar to the findings using periapical healing as an outcome measure, teeth with root fillings that were flush [(Dammaschke *et al*. 2003, Alley *et al*. 2004, Stoll *et al*. 2005)] or slightly short [(Dammaschke *et al*. 2003)] of the radiographic apex were found to be associated with a significantly higher probability of survival after 5 or 10 years. Whilst, Caplan & Weintraub (1997) observed similar trends, their findings were not statistically significant. In their case-control study, the proportion of long root fillings was higher amongst extracted teeth (31%) than amongst surviving teeth (24%). Whereas, the proportion of short root fillings was lower amongst the extracted (15%) than the surviving (19%) teeth.

ii) Quality of root filling

Reports on the effect of quality of root filling on tooth survival have been conflicting. Using survival of root filling as an outcome measure, including extraction of the tooth, replacement of the root filling or periradicular surgery as failure events, Stoll *et al*. (2005) found a significant effect of quality of root fillings. This was in contrast to the findings of a recent retrospective survey [(Tickle *et al*. 2008)], where the survival of root fillings placed within 12 National Health Service practices in the North West of England was not influenced by the technical quality of root fillings. The outcome information was only abstracted from patients' records and any extraction or re-treatment carried out in other practices was not considered in their analyses; therefore the validity of their findings remains questionable. In these two studies, the log-rank test was used for comparing the outcomes of the qualities of root fillings without accounting for potential confounders.

Using solely loss of the root treated tooth as an outcome measure, Caplan *et al*. (2002) and Chen *et al*. (2008) found that root fillings with voids or poor quality had no significant influence on the survival of teeth. The number and proportion of cases with voids in root fillings in the former study were small (28/216). In an earlier study by the same group, this factor was not eligible for the final multiple regression analyses because there was a greater than 90/10 split in the frequency between root fillings without (95.4%) and with voids (4.6%) [(Caplan & Weintraub 1997)]. The lack of influence by the quality of root filling reported by Chen *et al*. (2008) has been attributed to the fact that the majority of the root treated teeth were extracted due to problems of non-endodontic origin.

1.9.3.5 Post-operative prognostic factors

i) Type of coronal restoration

Teeth with the highest survival rates were those that were permanently restored within ninety days following root canal treatment (Mindiola *et al*. 2006). Teeth restored with a permanent restoration (Lazarski *et al*. 2001, Dammaschke *et al*. 2003, Lynch *et al*. 2004), crown (Lazarski *et al*. 2001, Aquilino & Caplan 2002, Caplan *et al*. 2002, Salehrabi & Rotstein 2004), or extra-coronal restoration (Tickle *et al*. 2008) were associated with a significantly higher chance of survival than their counterparts. These findings were corroborated by a recent systematic review (Stavropoulou & Koidis 2007). They found a 10-year survival for crowned-teeth to be 81%±12% which was higher than that for teeth restored with a direct restoration (resin composites, amalgam, cements) (63%±15%). Although the authors have quite rightly pointed out the difficulties in undertaking meta-analysis of retrospective data as the study characteristics or reporting methodology were not standardized, the degree and source of statistical heterogeneity were not explored.

Teeth restored with plastic restorations or, direct composite restorations had a higher chance of tooth survival over 5 years than those restored with amalgam or temporary cement (IRM®) (Nagasiri & Chitmongkolsuk 2005). This was in contrast to the findings by Dammaschke *et al*. (2003) who concluded that teeth restored with composite, amalgam or temporary cement had similar 10-year survival probabilities.

For those teeth restored with a crown, the time between root filling and core placement (Aquilino & Caplan 2002) and the use of post for retention (Caplan & Weintraub 1997, Aquilino & Caplan 2002, Caplan *et al*. 2002, Salehrabi & Rotstein 2004) had no significant influence on tooth survival. Lazarski *et al*. (2001), however, reported that teeth with prefabricated posts had a higher chance of survival than those with cast post & cores.

Teeth with single unit crowns were found to have a higher chance of tooth survival than teeth used as a bridge (Lazarski *et al*. 2001) or denture (Alley *et al*. 2004) abutment. Furthermore, root treated teeth used as bridge abutments had a lower chance of survival than those used as denture abutments (Alley *et al*. 2004). In stark contrast, Wegner *et al*. (2006) reported higher failures for removable prostheses abutments compared with fixed prostheses abutments. The discrepancy might be attributed to the fact that in the latter study, all the prostheses were retained with a post, made within the department, and the failure of the post and fracture of the tooth were also considered as failure events.

ii) Number of proximal contacts

The number of proximal contacts may predict the distribution of occlusal loading imposed on a tooth. Root treated teeth with two proximal contacts were found to be associated with a higher chance of survival after treatment (Caplan & Weintraub 1997, Caplan *et al*. 2002). Aquilino & Caplan (2002) found the same association but they did not include this factor in their final Cox regression model to investigate the effect of crown placement; this was because of confounding between the two variables: crown placement and proximal contacts. Curiously, in their other study (Caplan *et al.* 2002) aiming to investigate the effect of proximal contacts, both explanatory factors (crowned-teeth and 2 proximal contacts) were entered in the final model and proved to be significant at the 1% level. The effect of "crowned-teeth" (HR = 13.6) was more profound than the effect of "2 proximal contacts" (HR = 3.1). When only molar teeth with post-operative plastic restorations were analysed, the same relationship was found, although it was not statistically significant (Nagasiri & Chitmongkolsuk 2005). The fact that terminal molar teeth would have a maximum of one proximal contact might render investigation of this factor problematic. Root treated terminal teeth with pre-operative cracks were found to have a lower chance of 2-year survival than non-terminal teeth (Tan *et al.* 2006).

iii) Opposing dentition

In addition to number of proximal contacts, the dentition opposing the root treated tooth could also provide some crude information on occlusal loading of the tooth. Although their result was not statistically significant, Nagasiri & Chitmongkolsuk (2005) observed that teeth with no opposing natural teeth or with pontic of a removable prosthesis were associated with a higher chance of 5-year survival than those teeth opposed by natural teeth or pontic of a fixed prosthesis. They explained their insignificant findings by pointing out that occlusal reduction was performed during root canal treatment on teeth with thin remaining walls in order to minimize the effect of the opposing teeth. This effect should be negligible in the long-term because occlusal contacts will become re-established as a result of eruption of the unloaded teeth (Dahl & Krogstad 1982).

1.10 Conclusions of the literature reviewed

The principles for root canal treatment laid at the beginning of the last century are still consistent with contemporary quality guidelines provided by Endodontic societies in Europe and USA. Most of the stipulations in the guidelines are supported by clinical/microbiological evidence but not by gold standard long-term clinical outcome data. Despite the existence of long-term clinical outcome data for some aspects of the treatment procedures, the reported findings were often conflicting. Clinicians are therefore left with little evidence based guidance when choosing protocols for root canal treatment. The problem was found to be more severe for secondary than primary root canal treatment. The major problems with previous studies were related to insufficient sample size, and lack of sufficient data on intra-operative factors. Very often inappropriate statistical methods were used; in particular potential confounders were not accounted for in the analyses.

1.11 Aims and objectives of the present study

The present study had two main aims and was accordingly carried out in two parts: (1) to use a systematic approach to review, explore and synthesise the results of published available data (albeit heterogeneous); and (2) to carry out a prospective clinical study to investigate the effect of intra-operative factors on the outcome of root canal treatment (primary and secondary) after adjusting for significant pre- and post-operative factors.

The objectives were:

- **Part 1:** ***Systematic review of studies on primary and secondary root canal treatment:***
  - To examine the quality of available evidence.
  - To identify the factors showing significant influence on the success of primary and secondary root canal treatment, using periapical healing and tooth survival as outcome measures.
  - To explore the different approaches in addressing the issue of heterogeneity of the data from observational studies.
- **Part 2:** ***Prospective clinical study on the outcome of root canal treatment (primary or secondary):***
  - To assess and compare the success rate of primary and secondary root canal treatment after 2–4 years using absence of clinical and radiographic signs of periapical disease as the outcome measure and to evaluate the effect of intra-operative factors after accounting for potential confounders.
  - To investigate the *rate of reduction* in the size of periapical lesion within 4 years after treatment.
  - To investigate and compare the survival probability of teeth up to 4 years after primary or secondary root canal treatment and to identify the potential prognostic factors for tooth survival.

Chapter 2

Methodology

The present study was divided into 2 parts to address the selected research questions. The first part involved meta-analyses of outcome data from published clinical studies. The second part involved analyses of outcomes of primary and secondary root canal treatment by postgraduate students or staff in the Unit of Endodontology (UCL Eastman Dental Institute and UCLH Trust Eastman Dental Hospital, London, UK). The two outcome measures used for both parts of the study were: (1) absence of clinical and radiographic evidence of apical periodontitis (the shortened term: “absence of apical periodontitis” will be used throughout the rest of this Thesis); and (2) tooth survival. The association between the treatment outcomes and prospectively recorded data on pre-, intra-, and post-operative factors were analysed using logistic and Cox survival regressions.

Relevant research training and preparation for the MPhil/PhD programme commenced in Oct 1997 when the author was recruited to the position of Clinical Lecturer in Endodontology in the Department of Conservation Dentistry (later Unit of Endodontology from October 2004), Eastman Dental Institute. The author initially acquired knowledge and experience in design, execution, and data analysis for clinical studies in Endodontics through co-supervision of Endodontic Masters Research projects. The detailed time-line for research training, preparation, and different stages of work for the PhD programme is presented on the following page (Table 2.0).

2.0 Time-line for PhD programme

	Research training and preparation for PhD	Meta-analysis of published data	Prospective clinical study
10/1997	• Started as Clinical Lecturer in Endodontology at Eastman Dental Institute. • Provided training and supervision of data entry into pre- and post-operative data collection forms by postgraduate students. (The first version of the forms were designed by Richard Kahan & Kishor Gulabivala in 1996 and were officially launched in October 1997 after calibration [Saunders *et al.* 2000]). • Provided supervision of annual follow-up of completed Endodontic cases by postgraduate students. • Acquired knowledge and experience in clinical & laboratory research whilst co-supervising Endodontic Masters Research projects.		
11/2000	• Basic statistics course run by Department of Biostatistics, Eastman Dental Institute.		
10/2001	• Took over the annual follow-up of completed endodontic cases. • Audited the compliance in data recording by different operators using data collection forms.		
04/2002	• Practical statistics course for Medical Research run by Medical Statistics Unit, R&D Directorate, UCLH NHS Trust.		
08/2002	• Introduction to multilevel modelling by Professor Mark Gilthorpe.		
10/2002	• Redesigned and launched the 2nd version of data collection forms.		
11/2003	• Informal training on methods for meta-analysis by Dr. David Moles.		
01/2004	• **Registered for MPhil in Clinical Dentistry**	• Commenced systematic review of the outcome of 1^{o}RCT and 2^{o}RCT.	• Continued annual review of patients. • Commenced data extraction onto electronic database.
03/2004		• Completed reviews and commenced meta-analyses.	
01/2005		• Completed meta-analysis of data on the outcome 1^{o}RCT using AbAP as outcome measure.	
03/2005			• Preliminary analyses of data using AbAP as outcome measure.
04/2005	• Multilevel modelling workshop using MlwiN by Centre for Quantitative Social Science, University of Bristol.		
10/2006		• Preliminary meta-analysis of data on outcome of 2^{o}RCT using AbAP as outcome measure.	• Preliminary analyses of data using tooth survival as outcome measure.
11/2006	• **Upgraded from MPhil to PhD**		
01/2007		• Completed meta-analysis of data on outcome of 2^{o}RCT using AbAP as outcome measure.	
07/2007			• Completed review of patients.
09/2007	• Good clinical practice and the EU directive, UCH NHS Foundation trust (2001/20/EC).		
12/2007			• Completed data entry for the prospective study.
03/2008		• Completed meta-analysis of data on outcome of 1^{o} & 2^{o}RCT using tooth survival as outcome measure.	• Completed analyses of prospective clinical data.
08/2008	• **Completed PhD Thesis**		

1^{o}RCT = Primary root canal treatment; 2^{o}RCT = Secondary root canal treatment; AbAP = Absence of clinical and radiographic evidence of apical periodontitis.

2.1 Meta-analysis of data from previous clinical studies on success of primary and secondary treatment using absence of apical periodontitis as an outcome measure

2.1.1 Literature search

Longitudinal clinical studies investigating the outcome of primary root canal treatment, published up to the end of 2002, were identified electronically (MEDLINE database 1966 – 2002 Dec, week 4), and those investigating the outcome of secondary root canal treatment up to the end of 2006 (MEDLINE database 1966 – 2006 Dec, week 4). Six keywords were used for the search: (1) root canal treatment; (2) root canal re-treatment; (3) root canal therapy; (4) endodontic treatment; (5) endodontic re-treatment; (6) endodontics; (7) treatment outcome; and (8) success; with 12 strategies (1 AND 7, 1 AND 8, 2 AND 7, 2 AND 8, 3 AND 7, 3 AND 8, 4 AND 7, 4 AND 8, 5 AND 7, 5 AND 8, 6 AND 7, 6 AND 8). A Cochrane Library search was also conducted. PubMed was independently searched using the "related articles" feature. Four journals (International Endodontic Journal, Journal of Endodontics, Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics, Dental Traumatology [& Endodontics]) and bibliographies of all relevant papers and review articles were hand-searched. Unpublished studies were identified by searching abstracts and conference proceedings. Personal contacts were also used to identify ongoing or unpublished studies. Full articles were obtained for all relevant titles identified through either electronic or other search methods.

2.1.2 Study selection, quality assessment and data extraction

Three reviewers (Y-L Ng, K Gulabivala, S Rahbaran) independently assessed and selected the studies based on the following inclusion criteria:

1. Clinical study on root canal treatment;
2. Stratified analysis of primary and secondary root canal treatment available;
3. Sample size given and larger than 10;
4. At least 6-month post-operative review;
5. Success based on clinical and / or radiographic (strict = absence of apical radiolucency; loose = reduction in size of apical radiolucency) criteria;
6. Overall success rate given or could be calculated from the raw data;
7. Presentations in English, German, Chinese and Japanese languages were accepted.

Disagreements on study inclusion were resolved by discussion. The reasons for study rejection at this or subsequent stages were recorded.

Data were extracted by all three reviewers independently using custom-designed data collection forms. The data collection form was piloted on several papers and modified for optimal utility with agreement from all observers before final use. The data extracted could be classified into 6 groups; success rates, study characteristics, demographic data of patients, pre-, intra- and post-operative factors. Any disagreement was discussed and data were excluded if agreement could not be reached.

2.1.3 Estimation of pooled success rates

Stata version 9.2 statistical software (StataCorp LP, College Station, TX, USA) was used to perform all statistical analyses. Un-weighted pooled success rate by each factor was calculated by dividing the total number of successful units with the total number of units within the respective category (according to Hepworth & Friedman 1997). In addition, the weighted pooled success rates were estimated using random effects meta-analysis with DerSimonian and Laird's methods [DerSimonian & Laird 1986].

2.1.4 Estimation of effect of each clinical factor on success rate

The effect of each clinical factor on the success rate of primary and secondary root canal treatment was analyzed using 2 different approaches which involved calculation of:

1. Weighted pooled success rate by each factor under investigation (all relevant data accumulated from available studies), estimated using random effects meta-analysis with DerSimonean and Laird's methods (*In cases where data were only available from one study, the study reported success rate and 95% confidence interval was used*);

2. Weighted odds ratio for the factor under investigation on success rate, estimated using fixed and random effects meta-analysis. This analysis was restricted to studies providing complete partitioned data on success rates, enabling direct comparison of sub-categories of the factor investigated in the same study.

2.1.5 Assessment of statistical heterogeneity and its source

Statistical heterogeneity among the studies was assessed by Cochran's (Q) test [Cochran 1954] using the 10% significance level.

Meta-regression models [Thompson & Higgins 2002] were used to explore the potential sources of statistical heterogeneity and to assess the effect of factors on the pooled success rate. Factors (and their sub-categories) related to study characteristics considered in the meta-regression analyses as covariates were: decade of publication, study specific criteria for success (subcategories: radiographic; combined radiographic & clinical), unit of outcome measure (subcategories: tooth; root), duration after treatment ("at least 4 years", "less than 4 years"), geographic location of the study (subcategories: North American; Scandinavian; other countries), and qualification of the operator (subcategories: undergraduate students; postgraduate students; general dental practitioners; specialist or mixed group). A covariate was considered to be a potential source of heterogeneity when it was included in the meta-regression model and substantially (more than 10%) reduced: (1) the estimated proportion of total variation due to heterogeneity across studies (I^2); or (2) the estimated between-study variance (*tau*2), when compared with a model without the covariate.

2.2 Meta-analysis of previous data on primary and secondary root canal treatment using tooth survival as an outcome measure

2.2.1 Literature search

Longitudinal clinical studies investigating tooth survival following primary or secondary root canal treatment published up to the end of 2007 were identified electronically (MEDLINE database 1966 – 2007 Dec, week 4). Nine key terms were used for the search: (1) root canal treatment; (2) root canal re-treatment; (3) root canal therapy; (4) endodontic treatment; (5) Endodontic re-treatment; (6) endodontics; (7) treatment outcome; (8) success; and (9) survival; with 18 combination strategies (1 AND 7, 1 AND 8, 1 AND 9, 2 AND 7, 2 AND 8, 2 AND 9, 3 AND 7, 3 AND 8, 3 AND 9, 4 AND 7, 4 AND 8, 4 AND 9, 5 AND 7, 5 AND 8, 5 AND 9, 6 AND 7, 6 AND 8, 6 AND 9). A Cochrane Library search was also conducted. Four journals (International Endodontic Journal, Journal of Endodontics, Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics, Dental Traumatology [& Endodontics]) and bibliographies of all relevant papers and review articles were hand-searched. Unpublished studies were identified by searching abstracts and conference proceedings. Personal contacts were also used to identify ongoing or unpublished studies. Full articles were obtained for all relevant titles identified through either electronic or other search methods.

2.2.2 Study selection, quality assessment and data extraction

Two reviewers (Y-L Ng, K Gulabivala) independently assessed and selected the studies based on the following inclusion criteria:

1. Clinical study on root canal treatment;
2. Stratified analysis of primary and secondary root canal treatment available;
3. Sample size given and larger than 10;
4. At least 6-month post-operative review;
5. Success based on survival of tooth;
6. Overall survival probability given or could be calculated from the raw data;
7. Presentations in English, German, Chinese and Japanese languages were accepted.

Disagreements on study inclusion were resolved by discussion. The reasons for study rejection at this or subsequent stages were recorded.

Data were extracted by both reviewers independently using custom-designed data collection forms. The data collection form was piloted on several papers, modified for optimal utility and the final format agreed between the observers before final use. The data extracted could be classified into 6 groups; success rates, study characteristics, demographic data of patients, pre-, intra- and post-operative factors. Any disagreement was discussed and data were excluded if agreement could not be reached.

2.2.3 Estimation of pooled survival rates

The statistical method used to estimate the pooled survival rates were the same as estimation of pooled success rates in section 2.1.3.

2.2.4 Estimation of effect of each clinical factor on survival rate

The statistical method used to estimate the combined effect of clinical factor on survival rate was the same as in section 2.1.4.

2.2.5 Assessment of statistical heterogeneity and its source

Statistical heterogeneity among the studies was assessed by Cochran's (Q) test (Cochran 1954) using the 10% significance level. However, the source of heterogeneity could not be explored due to insufficient data on tooth survival.

2.3 Prospective clinical study to investigate the effect of various clinical factors on the outcome of primary and secondary root canal treatment

2.3.1 Ethical approval

This project was approved by the Joint Research & Ethics Committee of UCL Hospitals NHS Trust, Reference number 96/E195. Informed consent was obtained from all patients.

2.3.2 Inclusion criteria

The sample population of this study included all patients undergoing primary or secondary root canal treatment, that was commenced after the 1st October 1997 and completed by the end of June 2005 in the Unit of Endodontology (Department of Conservative Dentistry prior to 2004), UCL Eastman Dental Hospital, London, UK. The patients were referred from general dental practice, secondary dental or maxillo-facial referral centres and other Clinical Units of the dental hospital. All patients were age 15+ years old and had either primary or secondary root canal treatment completed with a permanent root filling and at least a semi-permanent restoration placed. The teeth were judged to have no pre-operative periodontal disease or prior surgical endodontic treatment.

2.3.3 Exclusion criteria

Teeth were excluded from this study if the apex/apices under investigation was/were not discernible on any of the periapical radiographs. The teeth were excluded from the analysis of "absence of apical of periodontitis" if: (1) they were followed-up for only one year; (2) they were extracted for reasons not related to endodontic problems; (3) information on the periapical status at the time of the extraction was not available; and (4) a completed pre- and intra-operative data collection form was not available for each tooth.

2.3.4 Primary and secondary root canal treatment in the unit of Endodontology

Endodontic postgraduate students were the main group of clinicians providing root canal treatment within the clinical unit. The student groups included one-year full-time Master of Science (MSc) students, two-year part-time MSc students, and 1st & 2nd year full-time Master of Clinical Dentistry (MCD) students (first cohort intake in Oct 1998).

The training of clinical technical skills begins during the introductory course when learning of basic protocols (Appendix II) was achieved through instruction, demonstration, and repeated cycles of practical work, feed-back and technical coaching. Basic root canal preparation technique using stainless steel instruments were learnt and refined through laboratory demonstrations and practical exercises on simulated canals in plastic resin blocks (Endo Vu®, Richard W. Pecina & Associates, Inc., IL, USA) and extracted teeth. Cold lateral compaction of gutta-percha technique using customization of master gutta-percha point (Van Zyl *et al.* 2005) was the main obturation technique taught during the introductory course. The main learning goals were to develop three-dimensional mental and visual interpretational skills, tactile skills and manual dexterity for: (1) detection of canal curvature and aberrations; (2) negotiation of fine canals through calcifications, natural or iatrogenic canal curvatures, and natural or foreign materials; (3) maintaining canal patency and curvature during preparation; (4) accurate gauging of canal diameter, with and without preparation; and (5) apical control of root filling placement. The importance of attention to detail during root canal treatment was also instilled during this preliminary course and then subsequently consolidated on the clinic. After the introductory course, students were provided self-directed learning opportunities to further refine the basic techniques on extracted teeth with difficult anatomies, aiming to achieve predictable and consistent results. Whereas, more advanced techniques (Appendix III) were learnt from interpretation of original protocols described in published papers, followed by testing the protocol on plastic training blocks and then extracted teeth. The end-point was the appreciation of: (1) limitations of protocols; (2) the importance of understanding the link between technical and biological aspects of root canal treatment; and (3) the importance of the value of tactile skills. The learning and skill-development journey therefore included the transition from protocol adherence to intuitive practice, a snap shot of skill ranges in the mixed student cohort would therefore include a spectrum of difference stages of development and proficiency.

The designated progressive stages for technical and clinical skill development (Appendix III) by the students would also be reflected in the used of a range of techniques, instruments and materials appropriate to their level. The details of treatment protocol are described in a later section on data management (Section 2.3.9).

The type and complexity of cases allocated for treatment by the students would be based on the individual's judged ability through on-going periodic assessment.

2.3.5 Follow-up appointments

The intention was to follow-up all the treated teeth annually upto 4 years post-operatively. Follow-up appointments were scheduled based on the month of the year when the treatment was completed. This information could be retrieved from the Endodontic patient database (Microsoft Office Access™, Microsoft Corporation, One Microsoft Way, Redmond, WA, USA) which was updated and maintained by the author as well as the Endodontic programme administrator under the author's supervision. The database was initially set up in 1996 by Dr. Richard Kahan who was formerly one of the part-time clinical teachers in the Unit. The main function of the database was to monitor the patient throughput by the Endodontic postgraduates. A list of teeth to be reviewed in each month was retrieved using the query function available from the Microsoft Office Access software™. Appointment letters were sent to the patients one month in advance of the appointment by the receptionists in the Division of Restorative Dentistry, under the instruction of the author. At the beginning of the study, 3 afternoon sessions per week were scheduled for reviewing the patients. This was subsequently reduced to 2 sessions per week. It was initially found that there was a 50% failure rate for recall attendance despite counselling this need prior to treatment acceptance. Therefore taking this into account, 20 patients were booked per session. Those patients failing to attend for recall were contacted with a personal courtesy call by the author and a further explanation letter to encourage them to attend follow-up appointments. The reasons for lack of attendance were recorded and analysed.

2.3.6 Follow-up clinical examination data

Follow-up examination consisted of general & endodontic history and, clinical & radiographic examination. All subjects were interviewed and examined by the author annually following completion of treatment. During the interview, the patient's personal, medical and dental details as well as the pre-operative pain history were confirmed. A detailed pain interview was conducted on patients presenting with pain to exclude any non-endodontic origin of the pain. Extra-oral examination included palpation of masticatory, neck and shoulder muscles for comparative tenderness, auscultation and palpation of the temporo-mandibular joint and assessment of the range of mandibular movement to exclude pain related to temporo-mandibular dysfunction syndrome. Clinical details about the treated tooth included, tenderness to percussion of the tooth, tenderness to palpation of adjacent soft tissues, presence of an associated sinus tract or swelling in the adjacent soft tissues, mobility of the tooth, periodontal probing profile around the tooth and the type & presence of an adequate coronal restoration and seal. The teeth adjacent to and opposing the tooth under investigation were also examined in order to exclude them as causes of pain or infection. If the tooth had been re-treated or extracted, the timing and reasons for re-treatment/extraction were recorded. The definitions for some of the above conditions are described in detail in a later section on data collection and management (Section 2.3.9).

2.3.7 Radiographic assessment of outcome

All the relevant radiographs (F-speed, Eastman Kodak Company, Rochester, NY USA): pre-operative, file at electronic apex locator (EAL) 'zero' length, master apical file at working length, post-obturation and follow-up periapical radiographs were taken reproducing the same angulation by intuitive orientation of a beam-aiming device (Rinn, Dentsply Ltd, Weybridge, UK) rather than occlusal registration record. In case of persistent discomfort from the treated tooth at follow-up, periapical radiographs at different horizontal angles were taken in order to detect any persistent radiolucent lesion superimposed upon the root. If the patient was pregnant at the time of the follow-up appointment, radiographic examination was deferred until after delivery.

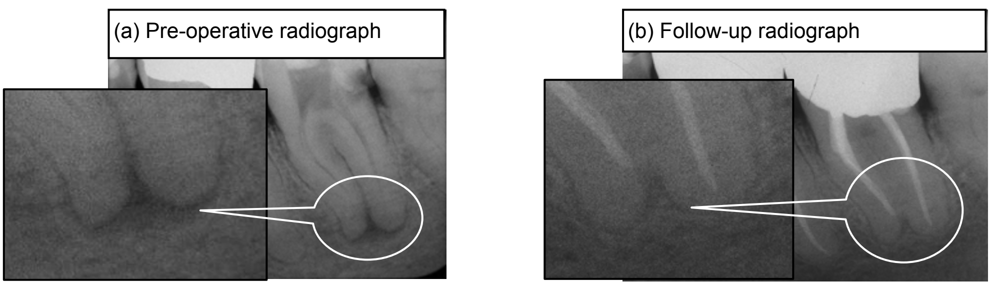
All the pre-operative, immediate post-obturation, and follow-up radiographs were viewed under standard conditions by the author using a fluorescent light box (Kenro Ltd, Swindon, UK) and a magnifying viewer (Brynolf, x 2.5 magnification, Trycare Ltd, Bradford, UK). The radiographs were mounted adjacent to each other in date order and viewed in a darkened room to determine the pre-operative periapical status and the radiographic healing pattern. The diameter of the lesion pre-operatively and at follow-up was measured using a metal endodontic ruler with precision upto 0.5 mm under x 2.5 magnification.

Thirty percent of the radiographs (randomly selected) were re-examined by the author one year later for intra-observer agreement assessment. A second observer examined 30% percent of the radiographs for inter-observer agreement assessment. The observers were blinded to the treatment procedures used.

The observers were pre-calibrated using reference radiographs (Figures 2.3.1–2.3.4) representing the 4 categories of radiographic healing pattern (these assessments were made for each root):

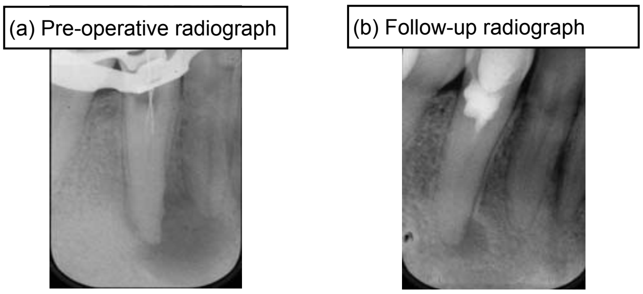
i. Complete – a normal periodontal ligament space.

Figure 2.3.1a&b Example of complete radiographic healing



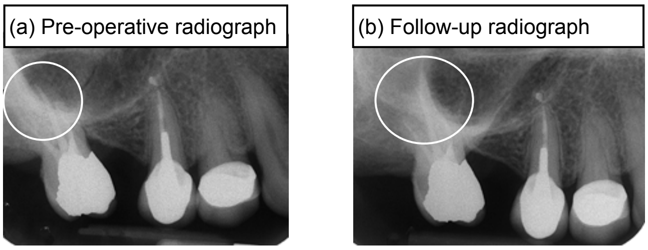
ii. Incomplete – a reduction in size of the lesion, but no return to normal periodontal ligament space width.

Figure 2.3.2a&b Example of incomplete radiographic healing



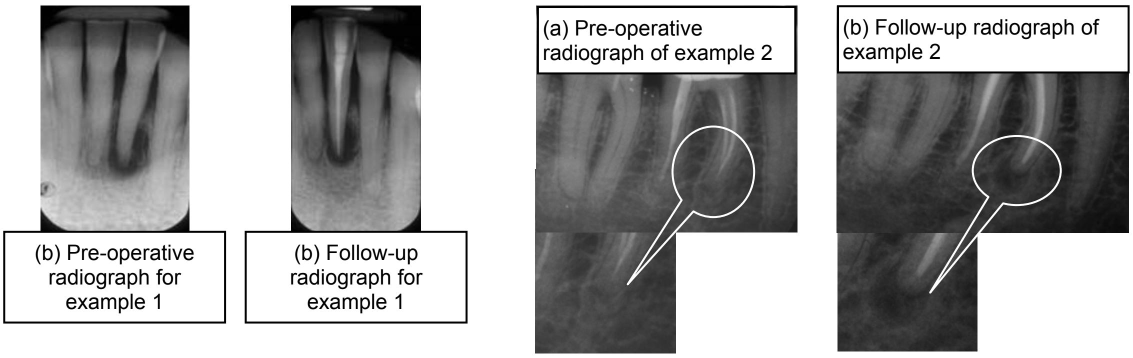
iii. Uncertain – radiographically impossible to make a definitive decision on status of post-operative healing.

Figure 2.3.3a&b Example of uncertain radiographic healing



iv. Failure – a previously existing periapical lesion had increased or remained at the same size or a previously normal periodontal ligament space had increased in width or developed into a radiolucent area.

Figure 2.3.4a–d Two examples of radiographic failure



Inter-observer agreement was assessed and in the event of disagreement, the two observers discussed their findings and agreed on the outcome. In case of no agreement, the final decision was made by the author.

2.3.8 Determination of outcome

The root was judged to be “free of apical periodontitis” when the patient / tooth demonstrated an absence of clinical evidence of periapical disease *and* complete radiographic healing.

The tooth was judged to have survived if it was still present and potentially functional at the time of follow-up, regardless of the clinical or radiographic findings. It was considered to have failed to survive if tooth had been extracted following treatment. Extraction might be reported by the patient attending the follow-up appointment, or reported by phone or letter by the patient or their general dental practitioners/referring dentist without the patient's attendance.

2.3.9 Data management

Comprehensive prospective pre- and intra-operative data for each patient had been meticulously recorded by Endodontic postgraduate students (under supervision by specialists) and staff on custom-designed data-collection-forms since October 1997. The forms were first introduced in 1997 after their initial validation (Saunders *et al.* 2000). After a subsequent audit of compliance in data entry, the forms were modified in 2002 by the author. The second version forms were designed to answer specific research questions intended to be addressed in this thesis (Appendix IV & V). The customized forms for recording information at follow-up appointments and radiographic assessment were also designed by the author (Appendix VI & VII).

Relevant demographic data, medical history, pre-operative pain history, diagnostic and treatment details of the tooth were extracted from the data collection forms and entered onto an electronic database (Microsoft Office Access software™) (Table 2.3.1–2.3.5). The Data protection act was complied with when handling patients' personal data. All the data were anonymized on the electronic database.

All the patient's medical conditions (Table 2.3.1) were self-reported onto a standard medical history form at the first consultation appointment; it was verified and updated by interrogation of the patient by the operator prior to treatment and at the follow-up appointment by the author.

Table 2.3.1 Demographic data, medical conditions and tooth / root type

Variables	Categories
Age	Continuous data (year)
Sex	0=female, 1=male
Medical history	Any condition or therapy reported by the patient were recorded
Long term antibiotics use	0=no, 1=yes
Patient has diabetes	0=no, 1=yes
Patient suffers from allergic reaction	0=no, 1=yes
Patient has systemic steroid therapy	0=no, 1=yes
Patient suffers from coronary heart disease/ hypertension	0=no, 1=yes
Patient is on hormone replacement therapy	0=no, 1=yes
Patient is on thyroxin therapy	0=no, 1=yes
Tooth type by FDI system	11–18 (teeth in right maxillary quadrant), 21–28 (teeth in left maxillary quadrant), 31–38 (teeth in left mandibular quadrant), 41–48 (teeth in right mandibular quadrant)
Tooth morphological type	0= maxillary incisor/canine, 1= maxillary premolar, 2= maxillary molar, 3= mandibular incisor/canine, 4= mandibular premolar, 5= mandibular molar
Tooth developmental anomalies	0=no, 1=yes
Root type	0=single, 1=buccal of 2-rooted, 2=palatal, 3=mesio-buccal, 4=disto-buccal, 5=mesial (mandibular molar), 6=distal (mandibular molar), 7= disto-lingual (mandibular molar)

Any condition reported by the patient was recorded but only those conditions that appeared to be prevalent among the patient cohort or previously reported to have significant association with treatment outcome were analysed (Table 2.3.1).

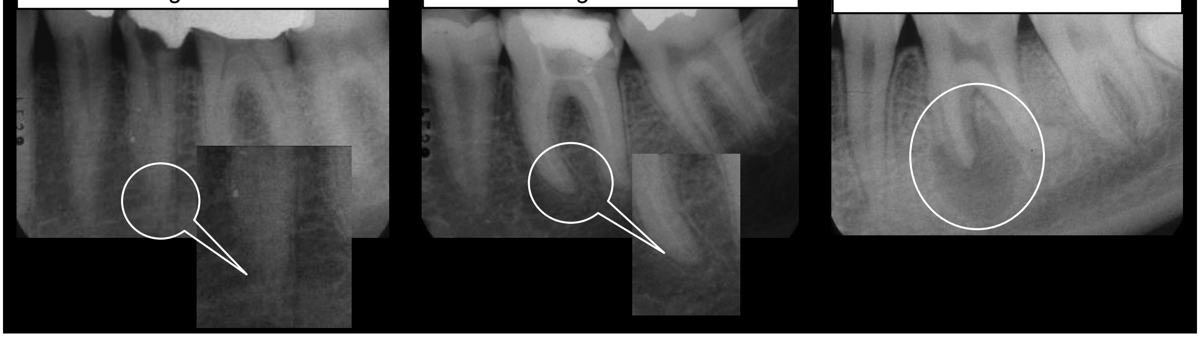
All the pre-operative data (Table 2.3.2) were recorded by the operators except the pre-operative periapical status, the size of the lesion and quality of previous treatment for each root; these were determined by the author.

Table 2.3.2 Pre-operative data

Variables	Categories
Pain	0=no, 1=yes
Crack or fracture	0=no, 1=fracture, 2=crack
Luxation injuries	0=no, 1=yes
Root fracture	0=no, 1=yes
Coronal filling	0=open, 1=temporary dressing, 2=plastic restoration, 3=cast restoration, 4=cast restoration with post
Tooth tender to percussion	0=no, 1=yes
Soft tissue tender to palpation	0=no, 1=yes
Sinus	0=no, 1=yes
Swelling	0=no, 1=yes
Pulpal status	0=non-vital, 1=vital (*presence of bleeding tissue upon accessing*)
Periodontal pocket of Endodontic origin	0=<5mm, 1=>=5mm, 2=extending to apex (*periodontal pockets judged to have a narrow profile*)
Periapical status	0=intact periodontal ligament (PDL) space, 1=widened PDL (*double the width of normal PDL*), 2=periapical lesion
Periapical lesion size	Continuous (mm) (*diameter of the lesion*)
Resorption	0=none, 1=internal, 2=external apical, 3=external lateral, 4=cervical
Quality of previous treatment	0=unsatisfactory, 1=satisfactory (*root filling extending to 2 mm within radiographic apex with no void*)
Canal content	0=uninstrumented, 1=instrumented but empty, 2=foreign material
Foreign material present in canal	0=$Ca(OH)_2$, 1=gutta-percha, 2=paste, 3=Thermafil, 4=silver point, 5=fractured instrument
Fractured instrument	0=none, 1=K-file, 2=H-file, 3=nickel-titanium instrument, 4=spiral filler
Perforation	0=none, 1=coronal (supra-osseous), 2=coronal (sub-osseous), 3=apical
Estimated endodontic prognosis	0=poor, 1=fair, 2=good
Estimated periodontal prognosis	0=poor, 1=fair, 2=good
Estimated restorative prognosis	0=poor, 1=fair, 2=good
Apical size of canal	Continuous (*ISO size of the largest file binding at the apical terminus prior to apical preparation*)

Peripapical status was classified into 3 categories (Figures 2.3.5a–c) and the diameter of the lesion was measured under x2.5 magnification using an endodontic metal ruler with 0.5 mm accuracy.

Figure 2.3.5a Intact periapical ligament
Figure 2.3.5b Widened periapical ligament
Figure 2.3.5c Periapical lesion



The quality of previous treatment was judged to be satisfactory if a well compacted root filling extending to within 2 mm from the radiographic root apex was present (Figure 2.3.6a&b).

Figure 2.3.6a Satisfactory previous treatment

Figure 2.3.6b Unsatisfactory previous treatment

Standard principles of primary and secondary root canal treatment were followed by the operators in the Unit of Endodontology but the execution of the treatment was not restricted to a single protocol. The relevant protocol details were however recorded as described below (Table 2.3.3 – Overleaf).

All the treatments were carried under local anaesthesia and rubber dam isolation. After accessing the tooth, the canals were prepared by pre-flaring the coronal (or straight) portion prior to negotiation of the apical portion and determination of working length. Sodium hypochlorite solution was always used as an irrigant during the pre-flaring procedure. The location of the apical terminus was always aided by an electronic apex locator (EAL); and this location was confirmed by taking a radiograph with a file placed at this position namely, the EAL “0” reading length (Table 2.3.3). The initial size of file (*recorded as the initial canal size*) was the largest that would reach EAL “0” reading length without force to ensure good electrical contact and stability when taking a radiograph. The apical extent of instrumentation was then determined by the operator as a distance equal to or short of the EAL “0” reading length (Table 2.3.3). In cases where canal terminus patency could not be achieved, a radiograph was taken with a small file placed to the most apically negotiable position in the canal. The apical extent of instrumentation for such cases was then measured as the discrepancy between the tip of the file and the radiographic apex by the author.

Operators were free to choose various types of instruments and technique of instrumentation for canal negotiation and shaping, albeit under supervised guidance appropriate to stage of development (Table 2.3.3). The choices available to each postgraduate student were approved by the programme director on the basis of their ongoing tactile skill assessments. The instruments available for use included: K-flex files (Dentsply Maillefer, Baillaigues, Switzerland), Flex-O-files (Dentsply Maillefer), Hedstrom files (Dentsply Maillefer), GT hand instruments (Dentsply Maillefer), ProTaper hand instruments (Dentsply Maillefer), rotary GT instrument system (Dentsply Maillefer), rotary Profile instrument system (Dentsply Maillefer), rotary ProTaper instrument system (Dentsply Maillefer) and rotary K3 instrument system

(SybronEndo, Orange, California, USA). The stainless steel instruments may have been used in filing (Abou-Rass & Bogen 1980), stem-winding (Backman *et al*. 1992) or balanced-force (Roane *et al*. 1985) motions. Patency of the apical terminus if achieved was maintained during canal enlargement by placing a small file of ISO size 8 or 10 passively to 0.5 mm beyond the apical terminus between each instrumentation step during canal enlargement.

Table 2.3.3 Intra-operative data

Variables	Categories
Type of treatment	0=1°RCT, 1=2°RCT
Operator code	Anonymous list with unique coding of each operator
Operator qualification	0=MSc/1st year MCD, 1=2nd year, 2=staff
Number of treatment visits	Continuous
Single or multiple visits	0=single, 1=multiple
Use of magnification	0=none, 1=loupes, 2=scope
Pre-operative foreign material removed?	0=None, 1=bypassed, 2=removed
Canal foramen patent	0=no, 1=yes
Working length (mm short of EAL '0' length)	Continuous
Type of canal preparation instrument	0=stainless steel, 1=hand NiTi, 2=rotary NiTi
Apical size of prepared canal	Continuous (ISO size)
Taper of prepared canal	0=.05, 1=.06, 2=.08, 3=.10, 4=.02, 5=.04
Perforation made?	0=no, 1=yes
Perforation repair material	0=no, 1=EBA/IRM, 2=GIC, 3=MTA
Canal blocked by operator?	0=no, 1=yes
Instrument fractured and left in canal?	0=no, 1=yes
Treated a second canal per root?	0=no, 1=yes
Missed any canal?	0=no, 1=yes
Type of irrigant used?	0=NaOCl, 1=NaOCl with other irrigant(s)
Concentration of NaOCl used?	0=2.5–3%, 1=4–5%
Use of Betadine®?	0=no, 1=yes
Use of Corsodyl®?	0=no, 1=yes
Use of EDTA solution?	0=no, 1=yes
Type of medicament	0=$Ca(OH)_2$, 1=Ledermix, 2=Antibiotics
Material for temporary (temp) restoration	0=IRM, 1=GIC, 2=temp crown, 3=temp post crown
Use of metallic band to protect tooth	0=no, 1=yes
Root filling technique	0=Cold lateral, 1=Warm spreader, 2=Energised spreading, 3=Schilder, 4=Continuous wave, 5=Obtura/Element, 6=MTA
Apical extent of root filling	Continuous data (mm ["-" =short; "+"=long])
Voids in apical 5 mm of root filling	0=no, 1=yes
Extrusion of sealer	0=no, 1=yes
Total hours of treatment	Continuous data
Inter-appointment pain	0=no, 1=yes
Inter-appointment swelling	0=no, 1=yes
Prescribed systemic antibiotics for treatment	0=no, 1=yes

1°RCT = primary root canal treatment; 2°RCT = secondary root canal treatment

The recommended minimum or optimal apical size of canal preparation was ISO size 30. If the initial apical size of the canal was larger than 30, it was not recommended to enlarge it further but the wall of the canal was gently planed using stainless steel instruments to facilitate disruption of the biofilm. After apical enlargement, the canal would be flared to various tapers: .04, .05, .06, .08, .10. (Table 2.3.1c). For large canals, it was not recommended to create a taper that would preserve root dentine. In this case a .02 taper was recorded and subsequently confirmed by the author during radiographic assessment. If the apical size of canal was larger than the largest available stainless steel instrument (ISO size 140), the canal size was estimated by the author from the pre-operative radiograph by measuring the diameter of the canal apically. Using stainless steel instruments for canal preparation, the tapers were restricted to .05 or .10 taper by introducing sequentially larger instruments at either 1.0 mm or 0.5 mm intervals coronally. Of course, this was conditional upon students appreciating gauging and understanding when to terminate instrumentation with a particular instrument. By definition, canals could only be shaped to .04, .06, .08, .10 tapers if nickel-titanium instruments with a matching taper was used. If ProTaper instruments exhibiting multiple tapers were used, the taper at the apical portion was recorded. For example, the apical taper of an ISO size 25 instrument is .08.

Sodium hypochlorite (NaOCl) solution (Teepol bleach, Teepol® products, UK) was the standard root canal irrigant. The operators were free to choose the concentration of the NaOCl (between 2.5% – 5.0%) and to use any additional irrigant as clinically perceived necessary and approved by supervisor (Table 2.3.3). They included 10% povidone-iodine (Betadine®, Seton Health Care PLC, Oldham, UK), 0.2% chlorhexidine gluconate (CHX) (Corsodyl®, Adam Health Care Ltd, UK), and 17% ethylene-diamine-tetra-acetic acid (EDTA) (AnalaR® grade, Merck BDH, Poole, UK). Canal irrigation was carried out using 27 gauge needles with side opening (Monoject® Luer lock syringe, Sherwood Medical, St. Louis, USA); with or without supplementation by ultrasonic agitation. Ultrasonic agitation was only used after mechanical canal enlargement was completed, fresh NaOCl irrigant was introduced into the canal and agitated using an ultrasonically energized ISO size 15 file (Dentsply Maillefer) with low power setting (EMS, Electro Medical Systems SA, Nyon, Switzerland or P5, Satelec Acteon group, Merignac, France).

Calcium hydroxide powder (BDH Merck, Poole, UK) mixed with sterile water was the standard inter-appointment medicament. Ledermix (Blackwell Supplies, Gillingham, UK) was occasionally used for teeth with acute pulpitis when extirpation of pulp tissues at the first visit was incomplete.

All the canals were filled with gutta-percha and Roth root canal cement (Roth Dental Company, Chicago, USA) using a technique of the operator's choice (Table 2.3.3). Customization of the tip of the master gutta-percha cone using chloroform (Chloroform BP, JM Loveridge Ltd, Southamptom, UK) was recommended as a routine measure (Van Zyl *et al.* 2005). A master gutta-percha cone of .02 taper (Kerr UK Ltd, Peterborough, UK) was used as the main core for lateral compaction technique. A master gutta-percha cones of various taper (QED, Peterborough, UK or ROEKO, Langenau, Germany) was used for the warm vertical compaction technique. The various techniques used included: cold lateral compaction technique, thermoplasticised lateral compaction with warm finger spreader, ultrasonically energised thermoplasticised lateral compaction technique, modified Schilder's warm vertical compaction technique (Van Zyl *et al.* 2005) and Continuous wave technique (Buchannan 1996). In some of the most recently completed cases, mineral trioxide aggregate (MTA) (ProRoot™ MTA, Dentsply, Weybridge, UK) was used as filling material for roots with large incompletely formed apies. When using the vertical compaction technique, a larger canal preparation taper was required (Schilder 1967).

The apical extent of and presence of voids within the apical 5 mm of root filling were determined by the author who assessed the post-obturation radiograph. The discrepancy between the tip of the file at the EAL "0" reading position and the apical extent of the root filling, was measured with the radiographic apex as the reference under magnification (x 2.5). The extrusion of sealer into the periapical tissue was also recorded. The fate of the extruded material was monitored with the follow-up radiographs.

Upon completion of root canal treatment, a permanent core was placed in the access cavity with or without an additional lining material (IRM® or glass ionomer cement), according to the operator's choice (Table 2.3.4). Amalgam was the core material usually used for posterior teeth, whilst composite was used to restore anterior teeth. A final radiograph was then taken by the operator and the final cast restoration, if indicated, was normally provided by the referring dentist, with some exceptions. If a cast post and core was required on an anterior tooth, the gutta-percha root filling was cut back leaving at least 5 mm of root filling apically, over which a layer of IRM® would be placed. The tooth was then temporarily restored with a temporary post-retained crown. If a cast post and core was indicated on a molar tooth, the pulp chamber was dressed with IRM® protected with a copper band and the final core and restoration were provided by the referring dentist. The type and quality of the final restoration was recorded by the author at the follow-up appointment.

Table 2.3.4 Post-operative restorative data

Variables	Categories
Core placed by whom?	0=GDP, 1=EDH/EDI
Type of core material?	0=amalgam, 1=composite, 2=glass ionomer cement, 3=cast post&core, 4=zinc oxide eugenol cement (IRM®)
Lining placed underneath core	0=none, 1=glass ionomer cement (GIC), 2=zinc oxide eugenol cement (IRM®)
Use of a post?	0=no, 1=yes
Final restoration by whom?	0=GDP, 1=EDH/EDI
Final restoration type at recall?	0=GIC/composite, 1=amalgam, 2=cast restoration, 3=temporary cement
Quality of final restoration at recall	0=obvious exposure of root filling material, 1=possible presence of marginal leakage, 2=satisfactory restoration

GDP = General dental practitioner;
EDH/EDI=specialist or trainees based at Eastman Dental Hospital or Eastman Dental Institute

Most of the data recorded at the follow-up appointment (Table 2.3.5) were self explanatory, except the quality of restoration.

Table 2.3.5 Data collected at follow-up appointment

Time of final recall after treatment	Continuous (Months after treatment)
Tooth survival at recall?	0=extracted, 1=present
Reason for extraction?	*Recorded in detail*
Time of extraction or time of last recall	Continuous data (Months after treatment)
Additional treatment since treatment completion	0=none, 1= non-surgical re-treatment, 2=surgery
Time of additional treatment	Continuous (Months after treatment)
Pain	0=no, 1=yes
Tooth fracture	0=no, 1=yes
Quality of restoration	0=exposed root filling, 1=possible leakage, 2=satisfactory
Sinus	0=no, 1=yes
Swelling	0=no, 1=yes
Adjacent soft tissue tender to palpation	0=no, 1=yes
Tooth tender to percussion	0=no, 1=yes
Root fracture	0=no, 1=yes
Periodontal probing depth	0=<5mm, 1=extent to mid-root level, 2=extent to the root apex
Periapical status by YL Ng	0=failed, 1=uncertain, 2=incomplete healing, 3=complete healing
Periapical status by K Gulabivala	0=failed, 1=uncertain, 2=incomplete healing, 3=complete healing
Diameter of periapical lesion at final recall	Continuous data (mm)
Time taken for lesion to heal	Years after treatment
Absorption of extruded sealer	0=complete absorption, 1=partial absorption, 2=no signs of absorption

The quality of restoration was classified into 3 categories:

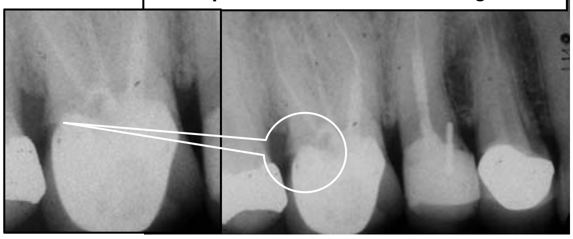
i. Obvious visual or tactile exposure of root filling material (Figure 2.3.7a&b) – the root filling could be seen or reached clinically by a probe through or past the restoration;

Figure 2.3.7a Example of obvious exposure of gutta-percha

Figure 2.3.7b Example of obvious exposure of gutta-percha

ii. Possible presence of coronal leakage (Figure 2.3.8) – a marginal discrepancy in the coronal restoration detected clinically by a probe or radiographically but no obvious visual or tactile exposure of the root filling to the oral cavity;

Figure 2.3.8 Example of possible presence of coronal leakage



iii. Satisfactory coronal restoration (Figure 2.3.9) – good retention and marginal fit of the restoration.

Figure 2.3.9 Example of satisfactory coronal restoration

2.3.10 Statistical analysis

Statistical analyses were performed with STATA version 9.2 (STATA Corporation: Texas 2005) statistical software package.

Consort type flow charts were used (CONSORT) (Altman *et al*. 2001) to show the number of samples included and lost at different stages of the study. They are generated separately for primary and secondary root canal treatment cases. The age and gender of the patients and the pre-operative pulpal and periapical status of the teeth which were excluded or lost at different stages were compared with those included for analysis.

Cohen's kappa coefficients were calculated to assess both intra- and inter-observer agreement on radiographic examination. The 95 % confidence interval was estimated using bias corrected bootstrap estimates (Reichenheim 2004). Good agreement was taken as >0.8, substantial as 0.61–0.8 and moderate as 0.4–0.6 (Petrie & Watson 1999).

The success of a treatment was assessed using two outcome measures. Treatment was defined as successful if the treated root showed absence of clinical and radiographic signs of apical periodontitis. Factors affecting the success of treatment were investigated. The loss of a tooth was defined as a second outcome measure and factors affecting the survival of the treated tooth were investigated.

2.3.10.1. Logistic regression to investigate prognostic factors for success defined as "*absence of apical periodontitis*"

Associations between potential prognostic factors and the ***absence of apical periodontitis*** after treatment were initially assessed using univariable logistic regression. To account for the clustering effect of multiple roots within the same tooth/patient or multiple teeth within patient, logistic regressions with cluster sandwich estimator for robust standard error was used in all of the logistic regression models. In case of a potential prognostic factor having more than two categories, the overall effect of the factor was assessed using Wald test to assess for heterogeneity.

Initial analyses were performed separately for primary and secondary root canal treatment to find potential prognostic factors, given that the two treatments may have different sets of prognostic factors due to a possible difference in nature of infection, and some factors were unique to secondary root canal treatment. Factors affecting success at the 5% significance level or showing a large effect (OR ≥ 1.5 or OR ≤ 0.5) at the 10% significance level were then entered simultaneously with "pre-operative periapical status" into logistic regression models one by one. The effect of those factors which remained significant at the 5% level or appeared to have a large effect at the 10% significance level, were further adjusted for "size of pre-operative periapical lesion" in models already including the "pre-operative periapical status".

The effect of type of treatment (primary/secondary) and its potential interaction with prognostic factors, identified from the analyses on separate datasets, was assessed in a combined dataset incorporating both primary and secondary treatments.

Using the combined dataset, the final model to investigate factors affecting the success of any type of root canal treatment was built as follows.

Potential prognostic factors, previously identified in the separate datasets, were entered one by one into logistic regressions including "pre-operative periapical status" and "size of pre-operative periapical lesion" to identify pre-operative, intra-operative and post-operative prognostic factors. A factor was considered to have prognostic value if the estimated odds ratio for the factor was significant at 5% or if the odds ratio exceeded 1.5 or was smaller than 0.5 at the 20% significance level in these models.

The final multiple logistic regression model was built through 3 stages:

1. All the ***pre-operative factors,*** having prognostic value from the previous models were entered together into the logistic regression model including the "type of treatment", "pre-operative periapical status" and "size of pre-operative periapical lesion". Those factors that lost their prognostic value, according to the above definition, were removed from the model.
2. All the ***intra-operative factors*** with prognostic values were entered into the model resulting from in stage 1. As in stage 1, those factors which lost their prognostic values in this model were removed.
3. Finally, all the ***post-operative factors*** *(Restoration after root canal treatment)* with prognostic values were added to the model resulting from stage 2 and retained according to the criteria given above.

Those factors which lost their prognostic value at any of the stages above were tested again in stage 3, if they appeared to have prognostic value in the final stage. Interaction between intra-operative factors and type of treatment was also explored in this last stage.

The goodness-of-fit of the final model was assessed using Hosmer and Lemshow method as well as through Pearson and deviance residuals. If the model is appropriate, the ratios of the sum of these squared residuals to the residual degree of freedom should be close to 1 (Hosmer & Lemshow 1980).

2.3.10.2. Survival analyses to investigate prognostic factors for success defined as "*survival of the tooth*"

When analyzing the ***survival of teeth*** after treatment, the event of interest was extraction of the tooth. The zero time point for these analyses was the date of completion of root canal treatment. Time to extraction of the tooth was recorded as the time interval (measured in months) between the date of the end of treatment and the date the tooth was extracted. Those teeth which were lost to follow-up (i.e. patients failing to return at the annual yearly recall but were examined at least once after treatment was completed) were censored at the patient's last visit to the clinic (if the tooth was not extracted at this visit). Those teeth that were followed up for 4 years, were censored at the 4 year recall date.

Cox proportional hazards regression models were used to investigate factors affecting the survival of the teeth after root canal treatment. Clustering within patients was accounted for by estimating robust standard error. The two datasets were combined for Cox regression analyses in order to increase the statistical power due to the small number of teeth lost after treatment. The type of treatment (primary, secondary) was included as a covariate in all models.

Initially, each of the potential prognostic factors was entered into a model simultaneously with "type of treatment" one by one. Those factors that proved to be significant at the 5% level or demonstrated a large effect ($HR \geq 1.5$ or $HR \leq 0.5$) but only significant at the 20% level were considered to have prognostic value and were selected for further multiple analyses.

The final multiple Cox regression model was also built through 2 stages:

1. All the potential significant factors related to ***patient's medical condition*** were simultaneously entered into a model together with "type of treatment". Those medical conditions that lost their prognostic value were removed from the model;
2. All the potential significant ***pre-, intra- & post-operative tooth factors*** were added to the model resulting from stage 1. Those factors which lost their prognostic values in this model were removed;

During the building of the multiple model, if a factor was considered on clinical judgment to be acting as a surrogate measure for another factor, and one (or both) lost their significance in the more complex model, the former factor was excluded from further analyses. If there was no reason for exclusion of either of the factors, they were analyzed separately in different models.

The proportionality assumption underlying the Cox regression was assessed using the Schoenfeld and scaled Schoenfeld residuals. This was done by graphical inspection and also by formally testing if the slope of a smoothed regression line of the scaled Schoenfeld residuals versus analysis time was different from zero. Those factors of which the effects seemed to change with time, an interaction term with time period was introduced into the model after splitting the time to have (approximately) equal numbers of failures in both time periods. If these interaction terms were significant (at $P < 0.10$), they were included in the final model; if not then the simpler model without interaction was used.

Chapter 3

Results

3.1 Meta-analysis of previous data on success rates of primary root canal treatment based on absence of apical periodontitis as the outcome measure

The results of the systematic review and meta-analysis were combined and have been published as a 2-part paper (Ng *et al*. 2007, Ng *et al*. 2008) (Appendix VIII)

3.1.1 Search results, study selection and data extraction

One hundred and nineteen papers were identified in the initial search, 51 articles were excluded for the reasons given in table 3.1.1 (page 103). Some papers presented different parts of the same study, so their data were combined for analyses in this review: (1) Heling & Tamshe (1970 & 1971); (2) Barbakow *et al*. (1980a&b & 1981); (3) Morse *et al*. (1983 a,b&c); (4) Ørstavik *et al*. (1987) & Eriksen *et al*. (1988). Conversely, Kerekes (1978) presented 2 separate data sets in their paper, and were therefore considered as 2 separate studies in this review. As a result, 63 studies fulfilling the inclusion criteria were selected for this review. The year of publication of the selected studies ranged from 1922 to 2002 with the highest number of studies published in the 1980's (n = 16) (Table 3.1.2, page 104).

Each reviewer had entered 174 data points per selected study and the initial agreement amongst the three reviewers was moderate (Kappa values 0.57-0.61). As per protocol, following discussion of the source of any disagreements, there was 100% concurrence on used data.

3.1.2 Methodological characteristics of selected studies

Of the 63 studies included in this review, only six were randomised controlled trials (Table 3.1.2, page 104). Others were cohort studies (n=8) or retrospective observational studies (n=49). Although 9 studies (Grahnén & Hansson 1961, Storms 1969, Selden 1974, Heling & Kischinovsky 1979, Pekruhn 1986, Sjögren *et al*. 1990, Friedman *et al*. 1995, Chugal *et al*. 2001, Hoskinson *et al*. 2002) had included previously root-filled teeth in their sample, they had provided stratified analysis for primary root canal treatment.

The recall rates (percentage of patients attending for follow-up after treatment) were reported by 39 studies and ranged from 11% to 100% with a median of 52.7%. Either root (27 studies) or tooth (36 studies) was used as the unit for outcome measure assessment. The sample sizes ranged from 22 to 2921 teeth or 38 to 2921 roots; some studies only included single-rooted teeth, hence the number of teeth and roots was the same.

The treatment outcome was determined by radiographic examination alone (27 studies) or in combination with clinical findings (36 studies) (Table 3.1.2, page 104). Different radiographic criteria of success have been used and these were divided into: "strict" (complete resolution of periapical lesion at recall) or "loose" (reduction in size of existing periapical lesion at recall). For the radiographic assessment of the outcome of treatment, only 19 studies (Table 3.1.2) employed at least 2 observers to carry out the assessment. Observer(s) were calibrated prior to evaluation of radiographs in 8 studies and intra- or inter-observer reliability tests were carried out in 9 studies (Table 3.1.2).

Different studies had evaluated the influence of a range of different clinical prognostic factors on outcome but the combinations of factors reported varied (Table 3.1.3, page 105).

The statistical methods used for analysing the association between potential influencing factors and treatment outcome were the chi-square test (31 studies), RIDIT (2 studies), logistic regression models (3 studies), ANOVA (2 studies), survival analysis (1 study), and logistic regression models using generalised estimating equations (1 study) (Table 3.1.2). Twenty-three studies did not analyse the data statistically or did not present such information.

3.1.3 Success rates by study characteristics

3.1.3.1 Outcome measure used

The reported success rates of root canal treatment ranged from 31% to 96% based on strict criteria and from 60% to 100% based on loose criteria. The weighted pooled success rates from studies using "strict" criteria (data available from 40 studies) were about 10% lower than those from studies using "loose" criteria (data available from 38 studies) regardless of use of radiographic examination alone or combined with clinical examination of outcome (Table 3.1.4, page 106). Some studies (n=14) presented the success rates stratified by both strict and loose criteria.

After pooling the data from the clinical and radiographic follow-up examination, the pooled success rates estimated by meta-analyses were 74.7% (95% CI 69.8%, 79.5%) from 40 studies using strict radiographic criteria, and 85.2% (95% CI 82.2%, 88.3%) from 36 studies using loose radiographic criteria. The estimated success rates by individual studies as well as the weighted pooled success rates by the two radiographic criteria are presented in Figures 3.1.1 & 3.1.2 (Pages 103–104). Meta-regression analyses showed the reported success rates based on strict radiographic criteria were 10.5% (4.4% - 16.7%, P = 0.001) lower than the success rates based on loose radiographic criteria. The radiographic criteria were also found to be responsible for part of the statistical heterogeneity, therefore the estimated success rates by individual factors were calculated separately for data based on the use of strict or loose criteria.

Table 3.1.1 Reasons for exclusion of the 51 articles

	Article	Inclusion criteria (1-6) *not* fulfilled or other reasons for exclusion
1	Grove (1921)	[1] Clinical study for primary root canal treatment
2	Hinman (1921)	[3] Sample size given [6] Overall success rate given or could be calculated
3	Grove (1923)	[1] Clinical study for primary root canal treatment
5	Rhein *et al.* (1926)	[4] At least 6-month post-operative review
6	Puterbaugh (1926)	[3] Sample size given [6] Overall success rate given or could be calculated
4	Coolidge (1927)	[6] Overall success rate given or could be calculated
7	Hall (1928)	[1] Clinical study for primary root canal treatment
8	Appleton (1932)	[4] At least 6-month post-operative review
9	Buchbinder (1936)	[2] Stratified analysis available
10	Macphee (1936)	[6] Overall success rate given or could be calculated
11	Strindberg (1956)	[2] Stratified analysis of 1^{o}RCT available
12	Frostell (1963)	[2] Stratified analysis of 1^{o}RCT available
13	Nicholls (1963)	[1] Clinical study for primary root canal treatment
14	Grossman *et al*. (1964)	[2] Stratified analysis of 1^{o}RCT available
15	Engström *et al.* (1964)	[2] Stratified analysis of 1^{o}RCT available
16	Ingle (1965)	[2] Stratified analysis of 1^{o}RCT available
17	Curson (1966)	[1] Clinical study for primary root canal treatment
18	Oliet & Sorin (1969)	[5] Success based on clinical and / or radiographic criteria
19	Storms (1969)	[2] Stratified analysis of 1^{o}RCT available
20	Ratliff (1973)	[5] Success based on clinical and / or radiographic criteria
21	Cvek *et al*. (1976b)	[2] Stratified analysis of 1^{o}RCT available
22	Adenubi (1978)	Same data set as Adenubi & Rule (1976)
23	Taintor *et al*. (1978)	[1] Clinical study for primary root canal treatment
24	Vernieks & Messer (1978)	[2] Stratified analysis of 1^{o}RCT available
25	Kerekes & Tronstad (1979)	[2] Stratified analysis of 1^{o}RCT available
26	Markitziu & Heling (1981)	[1] Clinical study for primary root canal treatment
27	Hession (1981)	[2] Stratified analysis of 1^{o}RCT available
28	Thoden van Velzan *et al*. (1981)	Same data set as Kerekes & Tronstad (1979)
29	Ashkenaz (1984)	[5] Success based on clinical and / or radiographic criteria
30	Seto *et al*. (1985)	[5] Success based on clinical and / or radiographic criteria
31	Ørstavik *et al*. (1986)	[6] Overall success rate given or could be calculated
32	Teo *et al*. (1986)	[2] Stratified analysis of 1^{o}RCT available
33	Kullendorff *et al*. (1988)	[1] Clinical study for primary root canal treatment
34	Molven & Halse (1988)	[2] Stratified analysis of 1^{o}RCT available Same data set as Halse & Molven (1987)
35	Augsburger & Peters (1990)	[4] At least 6-month post-operative review [5] Success based on clinical and / or radiographic criteria
36	Stabholz (1990)	[1] Clinical study for primary root canal treatment
37	Wong *et al*. (1992)	[5] Success based on clinical and / or radiographic criteria
38	Ørstavik & Hörsted-Bindslev (1993)	[6] Overall success rate given or could be calculated
39	Gutknecht *et al*. (1996)	[4] At least 6-month post-operative review
40	Friedman (1997)	[1] Clinical study for primary root canal treatment
41	Ricucci & Langeland (1997)	[1] Clinical study for primary root canal treatment
42	Weine & Buchanan (1997)	[1] Clinical study for primary root canal treatment
43	Shi *et al*. (1997)	[5] Success based on clinical and / or radiographic criteria
44	Weiger *et al*. (1998)	[1] Clinical study for primary root canal treatment
45	Caplan & White (2001)	[5] Success based on clinical and / or radiographic criteria
46	Oliver & Abbott (2001)	[1] Clinical study for primary root canal treatment
47	Waltimo *et al*. (2001)	[6] Overall success rate given or could be calculated
48	Lazarski *et al*. (2001)	[5] Success based on clinical and / or radiographic criteria
49	Lynch *et al*. (2002)	[5] Success based on clinical and / or radiographic criteria
50	Caplan *et al*. (2002)	[5] Success based on clinical and / or radiographic criteria
51	Murakami *et al*. (2002)	[4] At least 6-month post-operative review

1^{o}RCT=Primary root canal treatment

Table 3.1.2 Characteristics of studies selected

Author (Year)	Geographic location of study	[1]Study design	Recall rate (%)	≥ 4 year follow up after treatment	[2]Unit of measure	Sample size	[3]Assessment of success	[4]Radiographic criteria of success	≥ 2 radiographic observers	calibration	Reliability test	[5]Statistical analysis
1. Blayney (1922)	USA	R	28		T	104	C&R	L				
2. Auerbach (1938)	USA	R	22		T	211	C&R	L				
3. Buchbinder (1941)	USA	R	-		Ro	245	Ra	S				
4. Morse & Yates (1941)	USA	R	-		T	265	Ra	L				
5. Castagnola & Orlay (1952)	Sweden	R	68		T	1000	C&R	S				
6. Grahnén & Hansson (1961)	Sweden	R	44	✓	Ro	1277	C&R	S	✓			
7. Seltzer *et al.* (1963)	USA	C	-		Ro	2921	Ra	L				
8. Zeldow & Ingle (1963)	USA	C	-		T	42	C&R	L				
9. Bender *et al.* (1964)	USA	R	30		Ro	706	Ra	L	✓			
10. Engström & Lundberg (1965)	Sweden	R	74		Ro	181	Ra	S				
11. Harty *et al.* (1970)	UK	R	60		Ro	1139	C&R	S				X^2
12. Heling & Tamshe (1970 & 1971)	Israel	R	27		T	213	C&R	S				
13. Cvek (1972)	Sweden	R	-		Ro	55	Ra	S				ANOVA
14. Selden (1974)	USA	R	11		T	556	Ra	L				X^2
15. Werts (1975)	USA	R	23	✓	T	47	C&R	S				
16. Adenubi & Rule (1976)	UK	R	-		Ro	870	C&R	S				X^2
17. Heling & Shapira (1978)	Israel	R	17		T	118	C&R	S				
18. Jokinen *et al.* (1978)	Finland	R	45		Ro	2459	C&R	S	✓			X^2
19. Kerekes (1978)	Norway	R	-		Ro	379	Ra	S	✓			X^2
20. Kerekes (1978)	Norway	R	-		Ro	188	Ra	S	✓			X^2
21. Soltanoff (1978)	USA	R	-		T	266	Ra	L				
22. Heling & Kischinovsky (1979)	Switzerland	R	13		Ro	202	C&R	L				X^2
23. Barbakow *et al.* (1980a&b, 1981)	South Africa	R	60		T	335	C&R	L				X^2
24. Cvek *et al.* (1982)	Sweden	R	83	✓	Ro	45	Ra	S				X^2
25. Nelson (1982)	UK	R	-		T	299	C&R	L				X^2
26. Boggia (1983)	UK	R	-		T	52	Ra	S				
27. Klevant & Eggink (1983)	Holland	R	76		T	319	Ra	S				X^2
28. Morse *et al.* (1983a,b&c)	USA	R	-		Ro	458	C&R	L				X^2
29. Oliet (1983)	USA	C	-		T	338	C&R	L				X^2
30. Swartz *et al.* (1983)	USA	R	-		Ro	1770	C&R	L				X^2
31. Pekruhn (1986)	Saudi Arabia	R	81		T	925	C&R	S				X^2
32. Byström *et al.* (1987)	USA	C	56		Ro	79	Ra	S	✓			X^2
33. Halse & Molven (1987)	Norway	R	63	✓	Ro	551	Ra	S				X^2
34. Matsumoto *et al.* (1987)	Japan	R	38		T	85	C&R	L				X^2
35. Ørstavik *et al.* (1987) & Eriksen *et al.* (1988b)	Norway	RCT	36	✓	Ro	289	Ra	L		✓	✓	RIDIT
36. Safavi *et at.* (1987)	USA	R	-		T	464	C&R	S	✓	✓	✓	X^2
37. Åkerblom & Hasselgren (1988)	Sweden	R	73		Ro	64	C&R	S	✓			
38. Shah (1988)	India	C	70		T	65	C&R	L				
39. Sjögren *et al.* (1990)	Sweden	R	46	✓	Ro	573	Ra	S	✓	✓	✓	LR
40. Murphy *et al.* (1991)	USA	R	-		T	89	Ra	S				
41. Cvek (1992)	Sweden	R	76	✓	Ro	610	Ra	S				X^2
42. Reid *et al.* (1992)	Australia	RCT	44	✓	Ro	74	C&R	S	✓			X^2
43. Jurcak *et al.* (1993)	USA	R	58		T	102	C&R	L	✓			
44. Smith *et al.* (1993)	UK	R	54	✓	T	821	C&R	L				X^2
45. Peak (1994)	UK	R	-		T	136	C&R	S			✓	X^2
46. Friedman *et al.* (1995)	Canada	C	78		T	250	C&R	S				X^2
47. Çalişken & Şen (1996)	Turkey	R	-		T	172	C&R	S				
48. Ørstavik (1996)	Norway	C	81	✓	Ro	599	Ra	L		✓	✓	RIDIT
49. Peretz *et al.* (1997)	Israel	R	-		T	28	C&R	S				X^2
50. Sjögren *et al.* (1997)	Sweden	C	96	✓	Ro	53	Ra	S	✓	✓		
51. Lilly *et al.* (1998)	USA	R	-		T	22	C&R	S	✓			
52. Trope *et al.* (1999)	USA	RCT	-		T	102	Ra	S	✓	✓	✓	X^2
53. Ricucci *et al.* (2000)	Italy	R	-		T	110	Ra	S	✓			X^2
54. Weiger *et al.* (2000)	Germany	RCT	92		T	67	C&R	S	✓			LR
55. Chugal *et al.* (2001)	USA	R	75	✓	R	322	Ra	S	✓			LR
56. Deutsch *et al.* (2001)	USA	R	42		T	153	C&R	L				X^2
57. Heling *et al.* (2001)	Israel	R	-		T	319	Ra	L				ANOVA
58. Peak *et al.* (2001)	UK	R	-	✓	T	406	C&R	L			✓	
59. Pettiette *et al.* (2001)	USA	RCT	66		T	40	Ra	L				X^2
60. Benenati & Khajotia (2002)	USA	R	29		T	894	Ra	S				X^2
61. Cheung (2002)	Hong Kong	R	28	✓	T	282	C&R	S				Survival
62. Hoskinson *et al.* (2002)	UK	R	42	✓	Ro	413	C&R	S	✓	✓	✓	GEE
63. Peters & Wesselink (2002)	Holland	RCT	100		Ro	38	C&R	S	✓	✓	✓	X^2

UK = England, Scotland and Northern Ireland; ✓ = feature present
[1]R = Retrospective study, C = Prospective cohort study, RCT = Randomized controlled trial
[2]T = Teeth, Ro = Root (Unit of measure was recorded as 'root' for those studies which has only included single rooted teeth in their sample)
[3]C&R = Combined clinical and radiographic examination, Ra = Radiographic examination only [4]S = Strict criteria, L = Loose criteria
[5]LR = single level logistic regression, GEE = Generalized Estimating Equations, X^2 = Chi square test, RIDIT = Relative Incidence Distribution, ANOVA – Analysis of variance, Survival = Survival analysis

Table 3.1.3 Clinical prognostic factors reported by studies

Author (Year)	Gender	Age	Health	Tooth type	Pulpal status	Periapical status	Lesion size	Rubber dam used	Obstruction	Apical size	Canal taper	Irrigant	Medicament	Culture test	RF material & technique	Sealer	RF extent	Quality of RF	Acute flare up	Apical disturbance	No. of treatment visits	Restoration	Abutment
Blayney (1922)					✓	✓		✓				✓											
Auerbach (1938)					✓	✓						✓											
Buchbinder (1941)					✓	✓		✓				✓	✓	✓							✓		
Morse & Yates (1941)					✓	✓		✓				✓		✓							✓		
Castagnola & Orlay (1952)					✓	✓		✓													✓		
Grahnén & Hansson (1961)					✓	✓						✓			✓		✓				✓		
Seltzer *et al.* (1963)		✓			✓	✓								✓	✓		✓						
Zeldow & Ingle (1963)								✓				✓		✓	✓						✓		
Bender *et al*. (1964)					✓	✓								✓	✓		✓				✓		
Engström & Lundberg (1965)					✓								✓	✓							✓		
Harty *et al*. (1970)		✓						✓				✓					✓	✓		✓	✓		
Heling & Tamshe (1970 & 1971)					✓	✓		✓				✓	✓			✓	✓						
Cvek (1972)					✓	✓		✓				✓		✓							✓		
Selden (1974)					✓	✓	✓																
Werts (1975)					✓	✓																	
Adenubi & Rule (1976)	✓	✓		✓	✓	✓						✓	✓		✓	✓	✓	✓		✓	✓		
Heling & Shapira (1978)					✓	✓		✓					✓	✓	✓	✓	✓				✓	✓	
Jokinen *et al*. (1978)	✓	✓		✓	✓	✓							✓		✓		✓				✓		✓
Kerekes (1978)				✓											✓		✓	✓					
Kerekes (1978)				✓				✓							✓		✓	✓					
Soltanoff (1978)												✓			✓		✓				✓		
Heling & Kischinovsky (1979)					✓	✓		✓				✓	✓		✓	✓	✓						
Barbakow *et al*. (1980a&b, 1981)		✓		✓	✓	✓		✓					✓		✓	✓	✓				✓		
Cvek *et al*. (1982)					✓	✓		✓	✓			✓			✓								
Nelson (1982)		✓			✓	✓										✓	✓	✓		✓			
Boggia (1983)					✓	✓										✓	✓			✓	✓		
Klevant & Eggink (1983)								✓				✓	✓			✓	✓						
Morse *et al*. (1983a,b&c)					✓	✓						✓	✓		✓		✓				✓		
Oliet (1983)	✓	✓			✓	✓						✓			✓	✓	✓				✓		
Swartz *et al*., (1983)	✓	✓		✓		✓									✓		✓					✓	
Pekruhn (1986)					✓	✓		✓				✓				✓					✓		
Byström *et al*. (1987)					✓	✓		✓						✓	✓		✓				✓		
Halse & Molven (1987)					✓	✓									✓		✓						
Matsumoto *et al*. (1987)					✓	✓	✓	✓					✓	✓			✓				✓		✓
Ørstavik *et al*. (1987) & Eriksen *et al*. (1988b)					✓	✓						✓											
Safavi *et at*. (1987)					✓	✓						✓		✓	✓	✓					✓	✓	
Åkerblom & Hasselgren (1988)					✓	✓	✓	✓	✓			✓	✓		✓						✓		
Shah (1988)					✓	✓		✓							✓	✓					✓		
Sjögren *et al*. (1990)				✓	✓	✓	✓	✓				✓		✓	✓		✓	✓			✓		
Murphy *et al*. (1991)					✓	✓																	
Cvek (1992)					✓	✓									✓		✓				✓		
Reid *et al.* (1992)								✓					✓		✓	✓					✓		
Jurcak *et al*. (1993)				✓											✓						✓		
Smith *et al*. (1993)	✓	✓			✓	✓		✓			✓				✓	✓	✓				✓		
Peak (1994)				✓	✓	✓									✓		✓						
Friedman *et al*. (1995)					✓	✓						✓	✓		✓	✓							
Çalişken & Şen (1996)			✓		✓	✓	✓	✓				✓	✓		✓	✓				✓	✓		
Ørstavik (1996)					✓	✓		✓				✓											
Peretz *et al*. (1997)		✓			✓	✓																	
Sjögren *et al*. (1997)					✓	✓		✓				✓		✓	✓						✓		
Lilly *et al*. (1998)			✓		✓	✓									✓	✓						✓	
Trope *et al.* (1999)			✓					✓				✓	✓		✓	✓					✓		
Ricucci *et al*. (2000)								✓				✓			✓							✓	
Weiger *et al*. (2000)					✓	✓		✓				✓	✓		✓	✓					✓		
Chugal *et al*. (2001)					✓																		
Deutsch *et al*. (2001)					✓			✓				✓			✓	✓					✓		
Heling *et al*. (2001)					✓	✓						✓				✓	✓	✓				✓	
Peak *et al*. (2001)				✓	✓	✓									✓		✓						
Pettiette *et al*. (2001)					✓	✓																	
Benenati & Khajotia (2002)	✓	✓		✓												✓							
Cheung (2002)	✓	✓		✓	✓	✓		✓					✓		✓	✓					✓		
Hoskinson *et al*. (2002)	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓			✓	✓					✓	
Peters & Wesselink (2002)			✓		✓	✓		✓				✓	✓	✓	✓	✓					✓	✓	
Total	**8**	**13**	**4**	**13**	**51**	**49**	**6**	**33**	**2**	**1**	**2**	**32**	**20**	**14**	**38**	**25**	**29**	**7**	**0**	**5**	**35**	**8**	**2**

RF = Root filling ✓ = feature reported

Table 3.1.4 Estimated success rates by study characteristics

		Strict radiographic criteria				Loose radiographic criteria			
				Estimated Pooled Success rates				Estimated Pooled Success rates	
Factor / categories	*No. studies Identified	No. studies	No. units	[a]Un-weighted (%)	[b]Weighted (%)	No. studies	No. units	[a]Un-weighted (%)	[b]Weighted (%)
Outcome measure used									
Radiographic	27	17	4745	74.4	74.1 (66.9, 81.3)	14 (13)**	7177	83.4	84.1 (79.0, 89.3)
Clinical + Radiographic	36	23	10799	72.8	75.0 (68.4, 81.7)	24 (23)**	10430	82.0	85.8 (81.8, 89.9)
Duration after treatment (months)									
6	4	2	1120	17.3	29.6 (14.2, 73.3)	2	4633	89.1	89.1 (78.8, 99.5)
12	9	5	2080	68.6	67.7 (39.0, 96.4)	4	798	76.7	69.5 (52.3, 86.6)
24	6	3	2328	75.8	67.3 (43.8, 90.9)	3	1103	82.7	82.5 (75.2, 89.8)
36	5	2	941	80.4	80.6 (78.0, 83.1)	3	254	69.3	66.6 (36.1, 95.9)
48	6	5	2931	84.5	83.8 (79.3, 88.3)	2	301	93.5	61.7 (25.0, 96.0)
> 48	9	8	1162	86.8	85.4 (80.3, 90.6)	1	821	84.3	84.3 (81.8, 86.8)
Year of publication									
Before 1960	5	2	1245	68.2	68.2 (65.6, 70.8)	4	1580	82.2	84.2 (72.2, 96.1)
1960s	5	2	1458	81.3	79.7 (74.0, 85.4)	3	3669	80.4	80.4 (79.2, 81.7)
1970s	12	9	5468	69.8	79.0 (66.7, 91.3)	6 (5)**	4400	77.0	84.0 (71.3, 96.6)
1980s	16	9	2834	77.8	74.8 (62.5, 87.0)	10 (9)**	3770	89.7	88.2 (85.0, 91.4)
1990s	14	10	2007	83.9	76.9 (69.7, 84.1)	8	2271	83.3	85.5 (80.2, 90.9)
2000s	11	8	2532	65.2	68.0 (60.5, 75.4)	7	1917	85.2	85.1 (78.0, 92.3)
Geographic location of study									
USA or Canada	24	9	2412	67.5	74.1 (64.9, 83.2)	20 (19)**	9393	86.5	88.1 (84.9, 91.2)
Scandinavian country	15	12	6435	71.5	80.5 (71.1, 89.8)	3 (2)**	3347	70.4	70.3 (61.3, 79.2)
Other country	24	19	6697	76.9	71.2 (64.4, 78.1)	15	4867	83.4	84.5 (80.4, 88.5)
Qualification of operators									
Undergraduate students	21	14	8306	68.4	74.8 (67.0, 82.7)	11 (10)**	7808	79.9	83.3 (75.8, 90.9)
GDP	7	6	1353	64.4	65.7 (56.3, 75.1)	5	1228	85.5	86.2 (82.9, 89.5)
Postgraduate students	4	4	1336	82.9	77.2 (64.5, 89.8)	2	959	93.1	93.1 (91.5, 94.7)
Specialist	23	11	3288	87.6	84.8 (80.1, 89.4)	17 (16)**	6368	84.7	87.6 (83.9, 91.3)

*Total number of studies identified for the respective study characteristic is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation has been excluded.
[a] Un-weighted pooled success rates were estimated based on the Hepworth & Friedman (1997)'s approach.
[b] Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

Figure 3.1.1 Probability of success based on strict radiographic criteria

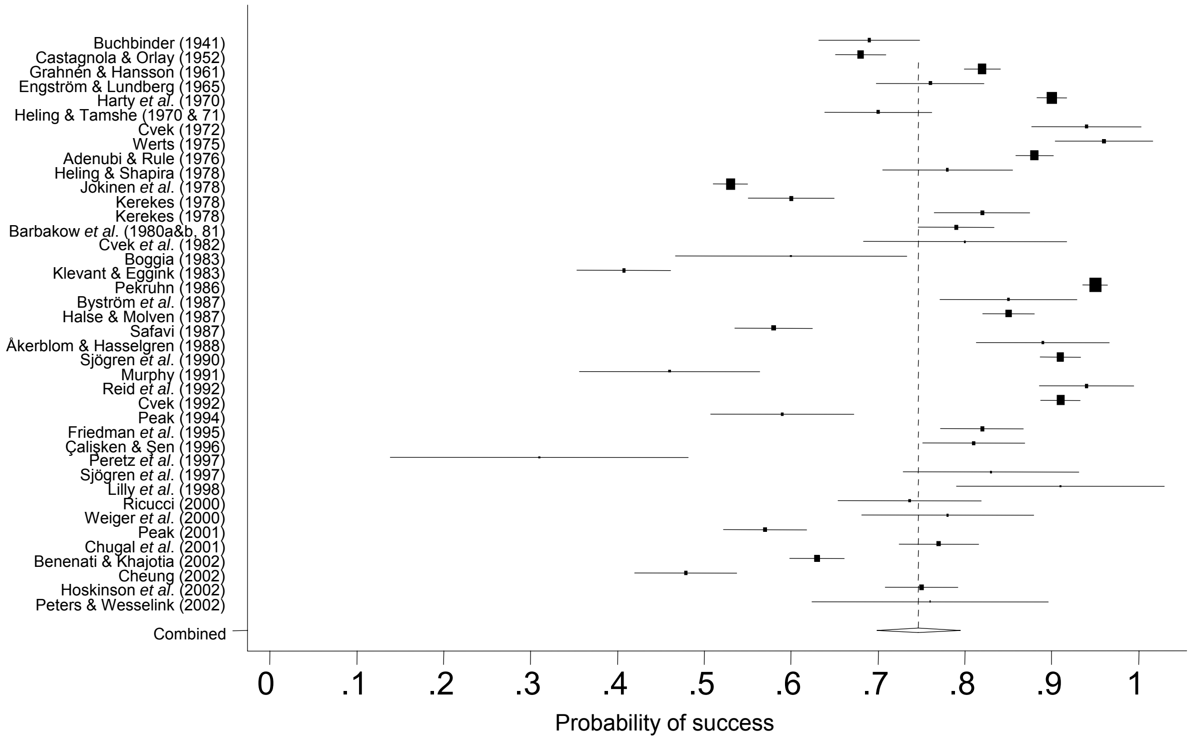
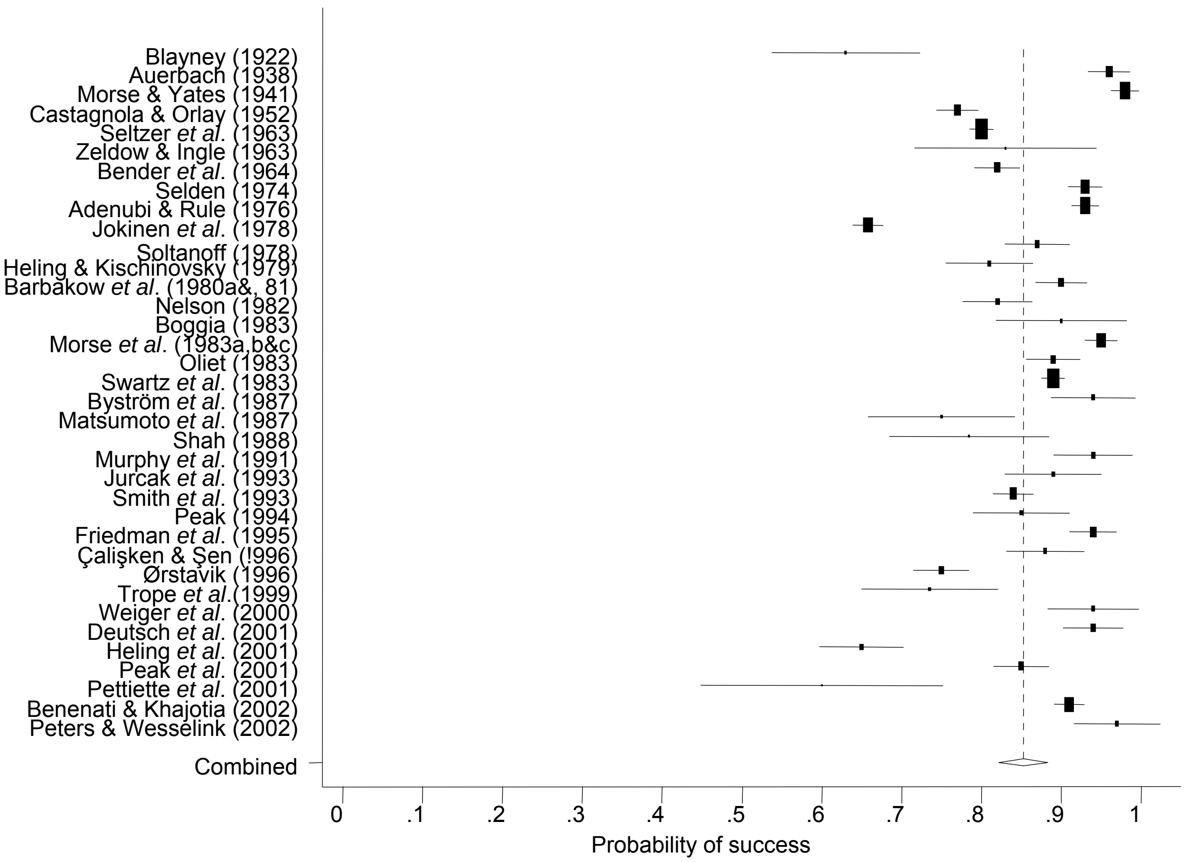


Figure 3.1.2 Probability of success based on loose radiographic criteria



3.1.3.2 Duration after treatment completion

Most studies did not standardize the duration after treatment completion when the outcomes were reviewed, which ranged from 6 months to 30 years. Only 15 studies (Table 3.1.2, page 104) followed-up all the cases for at least 4 years. Attempts to pool data on success rates by different follow-up durations are confounded by the relatively small study numbers in some groups, which may have produced distorted results. When strict criteria were used, the pooled success rates increased with longer follow-ups; the substantial increases were between 6 and 12 months and between 24 and 36 months after treatment (Table 3.1.4, page 106). However, there was no obvious trend in success rate by duration after treatment when loose criteria were used.

3.1.3.3 Year of publication

The pooled success rates based on “loose” outcome criteria for each decade since the 1920’s appeared to be similar with the highest pooled success rate at 88.2% during the 1980’s (Table 3.1.4). However, the pooled success rates based on “strict” outcome criteria for studies published during 1960’s (79.7%), and 1970s (79.0%) were the highest. More importantly, the expected trend of progressively increasing success rates over the last century was clearly not in evidence.

3.1.3.4 Geographic location of study

About a third of the studies were carried out in the USA or Canada (24 studies) and the rest were carried out in Scandinavian (15 studies, Sweden/Norway) or other countries/locations (24 studies) including: UK (8 studies), Israel (4 studies), Holland (2 studies), Switzerland (1 study), Australia (1 study), Germany (1 study), Hong Kong (1 study), India (1 study) , Italy (1 study), Japan (1 study), Saudi Arabia (1 study), South Africa (1 study) and Turkey (1 study) (Table 3.1.2). The studies performed in the North American countries reported the treatment outcome data more frequently based on loose radiographic criteria than on strict criteria. In contrast, most of the outcome data from the Scandinavian countries were based on strict rather than loose criteria. Based on the loose criteria, the pooled estimate of success rate of treatment carried out in Scandinavian countries (70.3%) was much lower than for those in North American (88.1%) or other (84.5%) countries; however, the pooled estimate for the Scandinavian countries, only consisted of two studies. In stark contrast, the pooled estimate of success rate from outcome data based on strict criteria from the Scandinavian countries (80.5%) was the highest (Table 3.1.4).

3.1.3.5 Qualification of operators (undergraduate, postgraduate, general dental practitioner, specialist)

The majority of the reviewed studies classified operator qualification as: undergraduate students (21 studies), general dental practitioners (7 studies), postgraduate students (4 studies) or specialists (23 studies). In 5 studies, treatment was carried out by a mixed group of operators and 3 studies did not provide this information. From the results, treatment carried out by postgraduate students and specialists had the highest weighted pooled estimate of success, regardless of strict or loose criteria (Table 3.1.4, page 106).

3.1.3.6 Source of heterogeneity

As the radiographic criteria for success had already been shown to have a significant effect on the pooled success rates, further meta-regression analyses were carried out separately on success rates based on strict or loose criteria. The purpose was to explore which of the other study characteristics were potentially responsible for the statistical heterogeneity. None of the other study characteristics had significant effects on the success rates reported by the studies or could account for the heterogeneity (Table 3.1.5) in estimating the pooled success rate of primary root canal treatment.

Table 3.1.5 Results of meta-regression analysis to account for the source of heterogeneity

	Strict		Loose	
Covariate included	I^2	*tau*2	I^2	*tau*2
No covariate included	**0.985**	**0.0247**	**0.973**	**0.0085**
Year of publication *(before 70's, 1970-1989, 1990-2002)*	0.983	0.0265	0.971	0.0098
Geographic location of study *(USA, Scandinavian or other countries)*	0.984	0.0244	0.952	0.0069
Unit of measure *(root or tooth)*	0.984	0.0253	0.961	0.0081
Qualification of operator *(specialist, postgraduate, undergraduate, GDP or mixed group)*	0.979	0.0209	0.974	0.0073
Criteria for success *(radiographic vs combined radiographic & clinical)*	0.986	0.0254	0.974	0.0088
Duration after treatment *(at least 4 years or shorter)*	0.985	0.0228	0.973	0.0085
Recall rate	0.986	0.0218	0.975	0.0117

I^2 = Proportion of total variation due to heterogeneity across studies; *tau*2 = Estimate of between-study variance
(If the I^2 and *tau*2 values were reduced by 10% after including a covariate in the regression model as compared with the values estimated without any covariates entered, the respective covariate was considered to be a potential source of heterogeneity)

3.1.4 Success rates by clinical factors

Amongst the 63 studies reviewed, none of the studies had evaluated *all* the clinical factors, consequently different aspects of data were missing from different studies (Table 3.1.3, page 105). Pre-selection of individual factors for analysis therefore gave a unique subset of the overall pool of studies that could vary substantially with the combination of factors under scrutiny. For each factor under investigation, the outcomes from each of the three approaches in analysis (section 2.1.4) are reported in their respective section. The results of analyses included: (1) estimated pooled success rates by each pre-, intra- and post-operative factor; (2) estimated combined effects (pooled odds ratios) for these factors; and (3) results of meta-regression analyses to explore the source of statistical heterogeneity.

3.1.4.1 Pre-operative factors

i) Gender

Only eight studies (Table 3.1.3) provided outcome data by gender. The pooled success rates for male patients were similar to those for female patients regardless of whether loose or strict criteria were used (Table 3.1.6). This is consistent with the pooled estimate of effects of gender (OR = 1.01; 95% CI 0.83, 1.23) (Table 3.1.7a). The heterogeneity 18.1 [7df, P = 0.011] was substantial but could not be explained by any of the study characteristics included in the meta-regression models.

ii) Age

In previous studies, the age groups were clustered into bands that varied between studies for the purposes of statistical analyses; direct comparison between studies therefore required some degree of intuitive interpretation.

Only thirteen studies (Table 3.1.3, page 105) reported outcome data by age. For the purpose of this review, the outcome data were pooled into 3 age bands: up to 25 years, 25 to 50 years and above 50 years. Although the differences were small, the pooled success rates decreased with increase in age regardless of whether strict or loose criteria for success were used (Table 3.1.6).

Table 3.1.6 Weighted pooled success rates (SR) by patient factors

Factor/categories	*Total no. of studies	Strict radiographic criteria			Loose radiographic criteria		
		No. of studies	No. of units	§Weighted pooled SR (%)	No. of studies	No. of units	§Weighted pooled SR (%)
Gender							
Male	8	5	2200	65.7 (48.3, 83.1)	6	2667	84.9 (75.9, 94.0)
Female	8	5	3044	65.1 (49.9, 80.2)	6	3537	85.2 (75.8, 94.6)
Age							
Below 25	13	7 (6)**	2873	68.3 (52.2, 84.4)	8	2243	86.9 (83.2, 90.7)
Between 25 and 50	11	5	2336	66.8 (50.5, 83.2)	7	1813	86.8 (83.2, 90.4)
Above 50	12	5	1159	65.6 (49.8, 81.4)	8	1880	84.1 (78.5, 89.7)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

Further meta-analyses showed no significant difference in the odds of success amongst the 3 age bands (Table 3.1.7b). No further meta-regression analyses were carried out as the heterogeneity was not significant.

Table 3.1.7a&b Summary of meta-analyses for the effects of patient factors on success rates of primary root canal treatment

Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity X^2 value	Heterogeneity P value
a) Gender					
Male vs Female	8	1.01	0.827, 1.23	18.1	0.011
b) Age					
<25 vs 25–50	10	0.95	0.84, 1.08	11.8	0.226
<25 vs >50	10	0.96	0.82, 1.12	9.8	0.371

iii) General medical health

There was insufficient stratified raw data for calculation of the pooled success rates by this factor.

iv) Tooth type

There was a wide variation in the manner of presentation of outcome data by tooth type in the various studies; the descriptors or classification used were: upper/lower teeth, anterior/posterior teeth, anterior/premolar/molar, 1/2/3 roots, 1/≥2 canals or each tooth type.

Thirteen studies (Table 3.1.3, page 105) presented the outcome data by tooth type (maxillary incisor & canine, maxillary premolar, maxillary molar, mandibular incisor & canine, mandibular premolar, mandibular molar); the differences in pooled success rates between the different tooth types were small, the mandibular premolar teeth had the highest success rates whilst the mandibular molar teeth had the lowest success rates based on strict criteria (Table 3.1.8).

Table 3.1.8 Weighted pooled success rates (SR) by tooth type

Factor/categories	*Total no. of studies	Strict radiographic criteria: No. of studies	No. of units	[§]Weighted pooled SR (%)	Loose radiographic criteria: No. of studies	No. of units	[§]Weighted pooled SR (%)
Tooth type							
Upper incisors and canines	13	9	2021	70.6 (54.7, 86.5)	7	2021	85.6 (75.5, 95.7)
Lower incisors and canines	12	8	523	66.6 (47.7, 85.5)	7 (6)**	512	85.1 (72.0, 98.3)
Upper premolars	12	8	918	70.1 (56.6, 83.6)	5	711	80.7 (70.4, 91.1)
Lower premolars	10	7	674	76.8 (64.9, 88.6)	5	490	86.2 (76.2, 96.1)
Upper molars	12	8	1327	75.0 (63.6, 86.5)	6	906	83.3 (75.1, 91.5)
Lower molars	11	7	1222	64.2 (47.4, 81.1)	6	1220	81.7 (73.1, 90.3)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.

** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.

[§] Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

When estimating the effect of tooth type, the outcome data from maxillary and mandibular teeth of the same morphological type were pooled together. The results showed that there was no significant difference in the odds of success amongst the three types of teeth: incisors/canines, premolars and molars (Table 3.1.9).

Table 3.1.9 Summary of meta-analyses for the effects of tooth type on success rates of primary root canal treatment

Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
Tooth type					
Premolars vs Incisors/canine	10	1.16	0.86, 1.57	29.5	0.001
Molars vs Incisors/canine	11	0.92	0.56, 1.51	98.0	<0.001

The statistical heterogeneity could be partly explained by the “criteria for success”, “unit of measure”, “geographic location of the study” and “year of publication” (Table 3.1.10a&b).

Table 3.1.10a&b Meta-regression analyses to account for heterogeneity in analysing the effects of tooth type on the success rate of primary root canal treatment

Covariate included	I^2	*tau*2
(a) Comparison of premolars vs incisors (n = 10)		
None	0.70	0.11
Criteria for success (loose or strict)	0.58	0.07
Unit of measure (root or tooth)	0.55	0.08
Geographic location of study (USA, Scandinavian or other countries)	0.20	0.01
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.74	0.16
Duration after treatment (≥4 years or not)	0.70	0.12
Year of publication (before 70’s, 1970-1989, 1990-2002)	<0.001	<0.001
(b) Comparison of molars vs incisors (n = 10)		
None	0.90	0.36
Criteria for success (loose or strict)	0.87	0.28
Unit of measure (root or tooth)	0.79	0.20
Geographic location of study (USA, Scandinavian or other countries)	0.15	0.04
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.90	0.37
Duration after treatment (≥4 years or not)	0.90	0.42
Year of publication (before 70’s, 1970-1989, 1990-2002)	0.32	0.42

I^2 = Proportion of variation due to heterogeneity; *tau*2 = Estimate of between-study variance

v) Pulpal and periapical status

v.i) Comparison of pre-operatively vital and non-vital teeth

A total of 51 studies provided success rates by pulpal status of the teeth. The pooled success rates for vital teeth were higher than those for non-vital teeth by 5% (loose criteria) or 9% (strict criteria) (Table 3.1.11).

Table 3.1.11 Weighted pooled success rates (SR) by pre-operative pulpal and periapical status

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	***Total no. of studies**	**No. of studies**	**No. of units**	**§Weighted pooled SR (%)**	**No. of studies**	**No. of units**	**§Weighted pooled SR (%)**
Pulpal / periapical (pa) status							
Vital pulp	22	13 (12)**	3027	82.5 (74.0, 91.0)	11 (10)**	1911	89.6 (83.1, 96.2)
Non-vital pulp	37	23	6343	73.1 (66.1, 80.0)	23	5928	84.7 (80.2, 89.2)
Non-vital pulp without pa lesion	15	9 (8)**	1699	82.1 (72.7, 91.6)	7	1141	90.1 (86.9, 93.3)
Non-vital pulp with pa lesion	48	28	4724	69.6 (61.1, 78.1)	29 (28)**	6844	81.4 (76.2, 86.6)
Size of periapical lesion							
≤ 5mm	6	4	488	80.2 (70.4, 90.0)	3	343	91.0 (84.6, 97.5)
> 5mm	5	3	308	78.8 (74.2, 83.3)	3	362	79.9 (66.1, 93.8)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

Out of the 63 studies reviewed, 19 had stratified success rates for both pre-operative vital and non-vital pulpal states but one study (Morse & Yates 1941) was excluded from the meta-analyses because of absence of root canal treatment failure in the vital pulp group. The odds of success of vital teeth were 1.77 (95% CI 1.35, 2.31) times higher than those for non-vital teeth (Table 3.1.12).

Table 3.1.12 Summary of meta-analyses for the effects of pre-operative pulpal and periapical status on success rates of primary root canal treatment

				Heterogeneity	
Comparisons (Test vs Reference categories)	**No. of studies**	**Odds ratio**	**95% CI**	**X^2 value**	***P* value**
Vital vs Non-vital	18	1.77	1.35, 2.31	61.6	< 0.001
Vital vs Non-vital without pa lesion	11	1.08	0.69, 1.67	33.5	< 0.001
Vital vs Non-vital with pa lesion	17	2.35	1.77, 3.13	53.6	< 0.001
Non-vital Without vs With pa lesion	13	1.95	1.35, 2.81	45.8	< 0.001
Small (≤5mm) vs Large (>5mm) pa lesion	5	1.55	0.85, 2.84	11.9	0.018

Pa = periapical

The heterogeneity in the data was substantial but could not be explained by the covariates investigated in meta-regression models (Table 3.1.13a).

Table 3.1.13a–e Meta-regression analyses to account for heterogeneity in analysing the effects of pulpal and periapical status on the success rate of primary root canal treatment

Covariate included	I^2	*tau*2
(a) Comparison of vital vs non-vital teeth (n = 18)		
None	0.72	0.22
Criteria for success (loose or strict)	0.74	0.19
Unit of measure (root or tooth)	0.74	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.68	0.26
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.71	0.35
Duration after treatment (≥4 years or less)	0.70	0.23
Year of publication (before 70's, 1970-1989, 1990-2002)	0.71	0.27
(b) Comparison of vital vs non-vital without periapical lesion (n = 11)		
None	0.70	0.19
Criteria for success (loose or strict)	0.67	0.24
Unit of measure (root or tooth)	0.72	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.58	0.21
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.61	0.17
Duration after treatment (≥4 years or less)	0.53	0.11
Year of publication (before 70's, 1970-1989, 1990-2002)	0.70	0.21
(c) Comparison of vital vs non-vital with periapical lesion (n = 17)		
None	0.70	0.34
Criteria for success (loose or strict)	0.69	0.23
Unit of measure (root or tooth)	0.72	0.39
Geographic location of study (USA, Scandinavian or other countries)	0.74	0.48
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.77	0.74
Duration after treatment (≥4 years or less)	0.72	0.41
Year of publication (before 70's, 1970-1989, 1990-2002)	0.62	0.62
(d) Comparison of non-vital teeth with or without periapical lesion (n = 13)		
None	0.74	0.18
Criteria for success (loose or strict)	0.71	0.15
Unit of measure (root or tooth)	0.67	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.65	0.26
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.80	0.33
Duration after treatment (≥4 years or less)	0.69	0.14
Year of publication (before 70's, 1970-1989, 1990-2002)	0.25	0.01
e) Comparison of small and large lesions (n=5)		
None	0.66	0.27
Criteria for success (loose or strict)	0.65	0.28
Unit of measure (root or tooth)	0.32	0.07
Geographic location of study (USA, Scandinavian or other countries)	0.82	0.78
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	-	-
Duration after treatment (≥4 years or less)	0.32	0.07
Year of publication (before 70's, 1970-1989, 1990-2002)	0.65	0.28

v.ii) Comparison of pre-operatively vital and non-vital teeth without periapical lesion

When comparing the pooled success rates between vital teeth and non-vital teeth without pre-operative periapical lesion, the difference was less than 1% regardless of whether strict or loose criteria were used (Table 3.1.11, page 113).

Out of the 63 selected studies, 11 studies had presented stratified outcome data for both of these pre-operative conditions and were included for estimation of the pooled odds ratio. The odds of success for vital teeth was similar to those for non-vital teeth without periapical lesion (OR = 1.08; 95% CI: 0.69, 1.67) (Table 3.1.12, page 113). The heterogeneity 33.5 [10 df] was significant. Meta-regression analyses showed that the covariate "geographic location of study" and "duration after treatment" were responsible for some of the heterogeneity (Table 3.1.13b, page 114).

v.iii) Comparison of pre-operatively vital and non-vital teeth with periapical lesions

The results for this group were in stark contrast to the previous groups; the pooled success rates of vital teeth were 8% (loose criteria) and 13% (strict criteria) higher than those of non-vital teeth with pre-operative periapical lesions (Table 3.1.11).

Out of the 63 studies, 18 studies had stratified outcome data by both pre-operative vital teeth versus non-vital teeth with periapical lesion. The paper by Morse & Yates (1941) was not included in the meta-analyses because of the absence of failed cases amongst the vital teeth group, leaving 17 studies in the meta-analysis (Table 3.1.12). The results showed that the odds of success of vital teeth was 2.35 (95% CI 1.77, 3.13) times higher than non-vital teeth with pre-operative periapical lesion (Table 3.1.12). The heterogeneity 53.6 [16 df] was substantial. However, none of the explored covariates was found to be responsible for the remaining heterogeneity as they neither reduced the I^2 or the *tau*2 values when they were entered separately into the meta-regression models (Table 3.1.13c, page 114).

v.iv) Comparison of pre-operatively non-vital teeth with or without periapical lesion

Of the non-vital teeth, the pooled success rates for those without periapical lesions were 9% (loose criteria) and 13% (strict criteria) higher than for those with periapical lesion pre-operatively (Table 3.1.11).

Of the 63 studies, 14 studies provided stratified outcome data by both non-vital teeth with and without periapical lesion. The paper by Sjögren *et al*. (1990) was not included in the meta-analysis because of absence of failed cases amongst the teeth without pre-operative periapical lesion, leaving 13 studies for the meta-analysis (Table 3.1.12). It was evident that non-vital teeth without periapical lesion had approximately 1.95 (95% CI 1.35, 2.81) times higher odds of success than non-vital teeth with periapical lesions (Table 3.1.12, page 113). The heterogeneity 45.8 [12 df] was substantial and could be partly explained by the "geographic location of studies" and "year of publication" (Table 3.1.13d, page 114).

v.vi) *Size of periapical lesion*

Only six reviewed studies (Table 3.1.3, page 105) provided the outcome data by the size of lesion. By pooling the data for lesion size into < 5mm or ≥ 5mm in diameter, the pooled success rate for small lesions was 11% (loose criteria) and 1% (strict criteria) higher than that for large lesions (Table 3.1.11, page 113). The estimated pooled odds of success for small lesions was higher but not statistically significant when compared to the pooled odds of success for large lesions (OR= 1.55; 95% CI 0.85, 2.84) (Table 3.1.12, page 113). The heterogeneity 11.9 [4df, P = 0.018] in the estimate was substantial and could be partly explained by "unit of outcome measure" and "duration after treatment" (Table 3.1.13d, page 114).

3.1.4.2 Intra-operative factors

i) Use of rubber dam isolation during treatment

Thirty-one studies reported the routine use of rubber dam during treatment whilst only 2 studies reported that rubber dam was not used. Twenty-eight studies did not mention the use of rubber dam isolation in their treatment protocol. There was no obvious difference in the pooled success rates between the treatments reported as carried out under rubber dam isolation or not (Table 3.1.14); lack of report of rubber dam use need not mean it was not used. The effects of use of rubber dam isolation could not be analysed further due to insufficient data.

Table 3.1.14 Weighted pooled success rates (SR) by use of rubber dam, apical size and taper of canal preparation

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	*Total no. of studies	No. of studies	No. of units	§Weighted pooled SR (%)	No. of studies	No. of units	§Weighted pooled SR (%)
Use of rubber dam isolation							
Yes	31	22	6353	78.0 (72.2, 83.8)	14	3729	84.4 (78.9, 90.0)
No	2	1	335	79.0 (74.6, 83.4)	2	400	82.5 (74.1, 96.4)
Apical size of canal preparation							
Small (ISO 20 – 30)	1	1	351	78.6 (76.4, 80.8)	0	-	-
Large (ISO 35 – 90)	1	1	53	69.8 (63.5, 76.1)	0	-	-
Taper of canal preparation							
Narrow	2	1	200	75.5 (72.5, 78.5)	1	534	82.2 (80.5, 83.9)
Wide	2	1	289	75.1 (72.6, 77.6)	1**	287	88.2 (86.3, 90.1)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.

** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.

§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

ii) Apical size of canal preparation

Only one study (Hoskinson *et al.* 2002) had presented the success rate by apical size of preparation; the study showed that success rate of small (ISO 20-30) apical preparations (77%) was higher than that of large (ISO 35-90) preparations (70%) (Table 3.1.14, page 116). The effects of size of preparation could not be analysed further due to insufficient data.

iii) Taper of canal preparation

Only two studies (Smith *et al.* 1993, Hoskinson *et al.* 2002) had presented the success rates stratified by taper of canal preparation (Table 3.1.14). The effect of taper of canal preparation could not be analysed further due to insufficient data.

iv) Canal obstruction and other technical errors

None of the previous studies had presented stratified outcome data for the effect of canal obstruction.

v) Irrigant

Some studies (n=32) standardised the use of irrigant, whilst others (10 studies) used a combination of irrigants; 20 studies did not present any information on irrigants. The pooled success rates by different irrigants are presented in table 3.1.15. There was no obvious trend in pooled success rates by the type of irrigant used. The effect of type of irrigant could not be analysed further due to insufficient data.

Table 3.1.15 Weighted pooled success rates (SR) by irrigant and medicament

Factor/categories	*Total no. of studies	Strict radiographic criteria: No. of studies	No. of units	§Weighted pooled SR (%)	Loose radiographic criteria: No. of studies	No. of units	§Weighted pooled SR (%)
Irrigant							
NaOCl	20	12	3374	79.3 (72.1, 86.6)	12 (11)**	3050	87.8 (82.4, 93.1)
Iodine	1	-	-	-	1	211	96.0 (93.4, 98.6)
Chloramine	1	-	-	-	1	104	63.0 (53.7, 72.3)
H_2SO_4	1	1	1277	82.0 (79.9, 84.1)	0	-	-
Water	2	1	1139	90.0 (88.3, 91.7)	1	42	83.0 (71.6, 94.4)
Saline	3	2	1189	64.4 (18.1, 100)	2	1136	90.3 (84.4, 96.1)
EDTA	3	2	258	72.2 (66.7, 77.6)	1	202	81.0 (75.6, 86.4)
Biosept	1	1	55	94.0 (88.0, 100)	0	-	-
Medicament							
Antibiotics	1	1	859	88.0 (85.8, 90.2)	1	859	95.1 (93.7, 96.6)
Antiseptics excluding $Ca(OH)_2$	9	6	1356	70.2 (55.5, 84.8)	4	671	85.6 (78.0, 93.1)
$Ca(OH)_2$	8	7	1106	75.0 (66.3, 83.8)	4	342	91.0 (86.3, 95.8)
Steroid	3	3	2221	67.5 (41.0, 94.0)	1	2142	67.0 (65.0, 69.0)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

vi) Medicament

Most studies did not standardise the type of root canal medicament used during treatment but the use of a number of medicaments has been reported. In descending order of frequency (by studies) of reported use, they are: calcium hydroxide (n=15), phenolic compound (n=8), iodine (n=4), creosote (n=3), cresatin (n=3), formaldehyde-based compounds (n=3), corticosteroid (n=3), antibiotics (n=2), Grossman's solution (n=1), and eugenol (n=1).

Twenty studies (Table 3.1.3, page 105) presented the outcome data based on the type of medicament. The pooled success rates of teeth dressed with steroid were lower than those dressed with antibiotics or antiseptics, regardless of whether strict or loose criteria were used (Table 3.1.15, page 117). No further analysis was carried out due to insufficient data.

vii) Root canal bacterial culture test results (positive or negative) prior to obturation

Fourteen studies (Table 3.1.3) provided information on treatment outcome related to the bacterial culture test results prior to root canal obturation. The pooled success rates for teeth with negative culture results were higher than for those with positive culture results by 7% (loose criteria) and 13% (strict criteria), respectively (Table 3.1.16).

Table 3.1.16 Weighted pooled success rates (SR) by pre-obturation root canal culture results

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	*Total no. of studies	No. of studies	No. of units	§Weighted pooled SR (%)	No. of studies	No. of units	§Weighted pooled SR (%)
Negative culture	13	9	1523	81.9 (71.6, 92.2)	6	2757	88.2 (83.3, 93.1)
No periapical lesion	*5*	*3*	*372*	*88.6 (85.4, 91.8)*	*3 (2)***	*1142*	*90.9 (86.2, 95.7)*
With periapical lesion	*10*	*7*	*578*	*73.1 (46.3, 100)*	*5*	*1555*	*86.8 (78.2, 95.5)*
Positive culture	8	4	99	68.5 (58.9, 79.5)	5	793	81.7 (79.0, 84.4)
No periapical lesion	*3*	*2*	*54*	*63.7(51.0, 76.4)*	*2*	*284*	*91.6 (88.3, 94.8)*
With periapical lesion	*5*	*3*	*45*	*73.6 (61.0, 86.2)*	*3 (2)***	*437*	*75.6 (71.5, 79.6)*

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

For those teeth without a pre-operative periapical lesion, the pooled success rate of teeth with negative culture results was 1% lower (loose criteria) and 24% higher (strict criteria) than those teeth with positive culture (Table 3.1.16). For those teeth with pre-operative periapical lesion, the pooled success rates of teeth with negative bacterial cultures prior to root filling were 11% higher (loose criteria) and 0.5% lower (strict criteria), respectively, than those of teeth with positive cultures (Table 3.1.16).

Of the 63 studies initially identified, 6 studies presented success rates by both positive and negative pre-obturation root canal culture results. Without stratifying the data for periapical lesion, the meta-analyses showed the odds of success of teeth with pre-obturation negative culture were not significantly different from those of teeth with a positive culture (OR 1.17, 95% CI 0.95, 1.44) (Table 3.1.17a – Overleaf). The heterogeneity (6.1 [5 df]) was not significant, therefore, no further meta-regression analysis was carried out.

Only 3 studies presented stratified success rates by both culture test results for teeth without periapical lesions. Meta-analysis results showed that there was no significant difference in success rates between teeth with negative or positive culture test results prior to obturation (OR 1.04, 95% CI 0.65, 1.64) (Table 3.1.17b). The heterogeneity 0.86 [2 df] was not significant and no further meta-regression analysis was carried out.

Although the difference was not statistically significant, the odds of success of teeth with pre-operative periapical lesion and negative culture were two times (OR 2.12, 95% CI 0.81, 5.53) higher than those for teeth with periapical lesions and positive culture results (Table 3.1.17c). The heterogeneity 4.0 [3 df] was not significant, and no further meta-regression analysis was carried out.

Table 3.1.17a–c Summary of meta-analyses for the effects of pre-obturation culture test results on success rates of primary root canal treatment

Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
a) -ve vs +ve culture results (any pa status)	6	1.17	0.95, 1.44	6.1	0.294
b) -ve vs +ve culture results (teeth with no pa)	3	1.04	0.65, 1.64	0.9	0.651
c) -ve vs +ve culture results (teeth with pa)	3	2.12	0.81, 5.53	4.0	0.135

viii) Root filling material and technique (single point gutta-percha, lateral condensation of gutta-percha, silver point, amalgam)

A number of root filling materials have been used in the studies, including: gutta-percha, silver points, amalgam, Hydron® (poly-hydroxyethyl methacrylate), Alytit® (Syrian asphalt dissolved in benzene), and iodoform paste. Most of the studies obturated the canals using gutta-percha with various types of sealer (24 studies) or gutta-percha softened in chloroform (chloropercha) (14 studies); one study used iodoform paste for obturation of all their cases. Most others (13 studies) used a combination of obturation materials or techniques and ten studies did not present any information on root filling material/technique.

Stratified data on success rates associated with root filling material/technique could be extracted from 38 studies (Table 3.1.3, page 105) and the pooled success rates are presented in table 3.1.18 (Overleaf). Teeth with chloropercha root fillings were associated with 1% (loose criteria) and 4% (strict criteria) higher pooled success rates than those teeth with lateral compaction of gutta-percha with sealer (Table 3.1.18).

Different types of sealer have been used, including: Zinc oxide eugenol-based (Bioseal®, Grossman® cement, Procosol®, Roth's root canal sealer®), resin-based

(AH26®), glass ionomer-based (Ketac Endo®), calcium hydroxide-based (CRCS®, Sealapex®) and paraformaldehyde-based (Endomethasone®). Zinc oxide eugenol-based sealers (14 studies) or AH26® (8 studies) were the most frequently used. Three studies did not standardize the use of sealer and 34 studies did not report this information. The pooled success rates for teeth filled with the resin based-sealer, AH26® had 0.8% higher (loose criteria) and 4.6% lower (strict criteria) success rates than those obturated with zinc oxide eugenol-based sealers (Table 3.1.18). The effects of root filling techniques, materials and type of sealers were not investigated further due to insufficient data.

Table 3.1.18 Weighted pooled success rates (SR) by root filling material and technique

Factor/categories	*Total no. of studies	Strict radiographic criteria			Loose radiographic criteria		
		No. of studies	No. of units	§Weighted pooled SR (%)	No. of studies	No. of units	§Weighted pooled SR (%)
Root filling material/technique							
Chloropercha	14	11	5766	80.0 (70.3, 91.4)	5	3136	86.9 (72.3, 99.2)
Lateral compaction of gutta-percha (GP)	23	13 (12)**	2986	76.0 (66.6, 85.4)	13	2556	85.8 (81.9, 89.7)
Single GP point	6	2	128	64.4 (56.2, 72.6)	5	2657	84.7 (79.7, 89.7)
Silver point	7	3	220	81.0 (67.0, 94.9)	3	1485	88.4 (83.6, 93.2)
Amalgam	1	-	-	-	1	162	85.2 (79.7, 90.7)
Sealer							
Zinc oxide eugenol-based	13	8	3991	75.3 (63.9, 86.6)	8	3724	86.5 (83.1, 89.9)
Resin-based	8	5	976	70.70(52.6, 88.7)	5	785	87.3 (76.3, 98.2)
Calcium hydroxide-based	2	2	239	80.2 (75.2, 85.3)	2	239	90.8 (84.9, 96.7)
Glass ionomer-based	1	1	250	82.4 (77.1, 86.9)	1	250	94.4 (90.8, 96.9)
Endomethasone	1	1	52	60.0 (46.7, 73.3)	1	52	90.0 (81.8, 98.2)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

ix) Apical extent of root filling

Most of the previous studies classified the various apical extents into three categories for statistical analyses: >2mm short of radiographic apex (short), 0-2mm within the radiographic apex (flush) and extruded beyond the radiographic apex (long). Without stratifying the data by presence/absence of periapical lesion, the pooled success rates by apical extent of root fillings revealed consistent trends regardless of strict or loose criteria: flush root fillings were associated with the higher success rate followed by short and then long root fillings (Table 3.1.19a - Overleaf).

The pooled success rates stratified by presence or absence of periapical lesion were then estimated. When there was no pre-operative periapical lesion, the pooled success rates of long root fillings were the lowest regardless of whether loose or strict criteria were used (Table 3.1.19b). When a periapical lesion was present, teeth with flush root fillings had the highest success rates whilst teeth with short root fillings had the lowest success rates (Table 3.1.19c).

Table 3.1.19a–c Weighted pooled success rates (SR) by apical extent of root filling

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	*Total no. of studies	No. of studies	No. of units	§Weighted pooled SR (%)	No. of studies	No. of units	§Weighted pooled SR (%)
a) Teeth with any periapical status							
Short RF	25	13	2106	76.8 (71.3, 82.3)	15	4112	82.5 (78.2, 86.7)
Flush RF	23	13	2874	77.3 (69.6, 85.0)	13 (11)**	4305	85.2 (80.0, 90.3)
Long RF	28	16	2599	65.8 (54.1, 77.5)	16 (15)**	2567	74.5 (67.9, 81.2)
b) Teeth with no periapical lesion							
Short RF	5	2	187	93.2 (89.6, 96.8)	3	673	89.9 (82.1, 97.7)
Flush RF	5	2	102	90.4 (77.0, 100)	3	682	92.3 (89.5, 95.2)
Long RF	5	2	180	83.2 (54.4, 100)	3	169	74.2 (67.6, 80.8)
c) Teeth with periapical lesion							
Short RF	10	4	234	69.9 (61.5, 78.3)	6	801	74.9 (66.1, 83.7)
Flush RF	8	4	331	83.7 (72.7, 94.7)	4 (3)**	844	84.2 (78.7, 89.6)
Long RF	11	5	290	73.6 (64.3, 83.0)	6	558	80.8 (70.2, 91.5)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

Twenty one studies (Table 3.1.20a) presented success rates stratified by **short or flush** root fillings. The meta-analyses showed that there was no significant difference in the odds of success (OR 1.27, 95% CI 0.93, 1.73) between teeth with short or flush root fillings when teeth with or without pre-operative periapical lesion were considered together (Table 3.1.20a). The heterogeneity (125.0 [20 df]) was significant and could partly be explained by the "qualification of operator" (Table 3.1.21a - Overleaf).

Table 3.1.20a–c Summary of meta-analyses on the effects of apical extent of root filling on success rates of primary root canal treatment

Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity X^2 value	Heterogeneity *P* value
a) Flush vs Short root fillings					
Flush vs Short (any pa status)	21	1.27	0.93, 1.73	125.0	< 0.001
Flush vs Short (teeth with no pa lesion)	5	0.83	0.55, 1.23	8.8	0.067
Flush vs Short (teeth with pa lesion)	7	1.56	1.26, 1.94	12.0	0.061
b) Flush vs long root fillings					
Flush vs Long (any pa status)	21	2.34	1.87, 2.93	56.1	< 0.001
Flush vs Long (teeth with no pa lesion)	5	3.72	2.48, 5.60	4.8	0.304
Flush vs Long (teeth with pa lesion)	7	1.74	1.36, 2.21	10.2	0.117
c) Short vs long root fillings					
Short vs Long (any pa status)	24	1.80	1.34, 2.42	117.6	< 0.001
Short vs Long (teeth with no pa lesion)	5	2.89	0.89, 9.08	26.3	< 0.001
Short vs Long (teeth with pa lesion)	9	1.06	0.84, 1.33	14.3	0.075

Pa = periapical

Similarly, no significant difference in the odds of success (OR 0.83, 95% CI 0.55, 1.23) was found between flush and short root fillings in teeth without a pre-operative lesion (Table 3.1.20a, page 121). However, when considering teeth with a pre-operative periapical lesion, those with flush root fillings had 1.6 times the odds of success (OR 1.56, 95% CI 1.26, 1.94) compared to teeth with short root fillings. Although the heterogeneity was significant at the 10% level, meta-regression analysis was not carried out to explore the source due to insufficient data.

Table 3.1.21 Meta-regression analyses to account for heterogeneity in analysing the effects of apical extent of root filling on the success rate of primary root canal treatment

Covariate included	I^2	*tau*2
a) Comparison of Flush vs Short RF (n = 21)		
None	0.84	0.45
Criteria for success (loose or strict)	0.84	0.47
Unit of measure (root or tooth)	0.83	0.47
Geographic location of study (USA, Scandinavian or other countries)	0.80	0.47
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.71	0.25
Duration after treatment (≥4 years or less)	0.85	0.48
Year of publication (before 70's, 1970-1989, 1990-2002)	0.86	0.62
b) Comparison of Flush vs Long RF (n = 21)		
None	0.64	0.18
Criteria for success (loose or strict)	0.64	0.18
Unit of measure (root or tooth)	0.65	0.17
Geographic location of study (USA, Scandinavian or other countries)	0.60	0.17
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.37	0.07
Duration after treatment (≥4 years or less)	0.64	0.16
Year of publication (before 70's, 1970-1989, 1990-2002)	0.65	0.18
c) Comparison of Short vs Long RF (n = 24)		
None	0.80	0.43
Criteria for success (loose or strict)	0.81	0.46
Unit of measure (root or tooth)	0.77	0.39
Geographic location of study (USA, Scandinavian or other countries)	0.75	0.36
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.78	0.38
Duration after treatment (≥4 years or less)	0.77	0.42
Year of publication (before 70's, 1970-1989, 1990-2002)	0.79	0.42

Twenty one studies (Table 3.1.20b) presented stratified outcome data by **long and flush** root fillings. The meta-analysis showed that the odds of success for teeth with flush root fillings was significantly higher than for those teeth with long root fillings (OR 2.34; 95% CI 1.87, 2.93) when periapical status was not considered (Table 3.1.20b). The heterogeneity 56.1 [20 df]) was substantial and could be partly explained by the "qualification of the operators" (Table 3.1.21b). Such a difference in the odds of success remained true even when teeth with or without pre-operative periapical lesions were considered separately in the meta-analyses (Table 3.1.20b).

Stratified outcome data by **short and long** root fillings were available from 24 studies (Table 3.1.20c, page 121). When teeth with different periapical status were considered together, the meta-analysis results showed that the odds of success for teeth with short root fillings were significantly higher than those for teeth with long root fillings (OR 1.80; 95% CI 1.34, 2.42) (Table 3.1.20c). The heterogeneity 117.6 [23 df]) was substantial but none of the tested covariates could account for it as they neither reduced the I^2 or the *tau*2 values when they were entered separately into the meta-regression models (Table 3.1.21c, page 122). When only teeth without pre-operative periapical lesion were considered, the OR increased to 2.89 (95% CI 0.89, 9.08), with the difference being borderline significant (P = 0.051). In contrast, when only teeth with pre-operative periapical lesion were considered, there was no difference in the odds of success between teeth with short or long root fillings (OR 1.06, 95%CI 0.84, 1.33) (Table 3.1.20c).

x) Quality of root filling

Seven studies provided stratified data by quality of root filling. The pooled success rates for teeth with satisfactory root fillings were higher than those for teeth with unsatisfactory root fillings by 18.7% (loose criteria) and 25.9% (strict criteria), respectively (Table 3.1.22a). Only 2 studies, each based on a single radiographic criterion, have presented data by quality of root filling with periapical lesion (Table 3.1.22b). This observation could be confirmed by the large & significant estimated pooled effects (OR = 3.92; 95% CI 2.26, 6.78) (Table 3.1.23 – Overleaf). The heterogeneity 27.6 [6df] in the estimate was substantial and could be partly explained by “year of publication” (Table 3.1.24 - Overleaf).

Table 3.1.22a&b Weighted pooled success rates (SR) by quality of root filling

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	*Total no. of studies	No. of studies	No. of units	§Weighted pooled SR (%)	No. of studies	No. of units	§Weighted pooled SR (%)
a) Teeth with any periapical status							
Satisfactory	7	5	2173	87.0 (82.3, 91.7)	3	1076	82.9 (70.4, 95.4)
Unsatisfactory	7	5	427	61.1 (50.4, 71.8)	3	116	64.2 (46.2, 82.1)
b) Teeth with periapical lesion							
Satisfactory	2	1	193	86.5 (81.7, 91.3)	1	169	63.9 (56.7, 71.1)
Unsatisfactory	2	1	11	81.8 (59.0, 100)	1	23	69.6 (50.8, 88.4)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

Table 3.1.23 Summary of meta-analyses for the effects of apical extent and quality of root filling on success rates of primary root canal treatment

Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
Quality of root fillings					
Satisfactory vs Unsatisfactory	7	3.92	2.26, 6.78	27.6	<0.001

Table 3.1.24 Meta-regression analyses to account for heterogeneity in analysing the effects of quality of root filling on the success rate of primary root canal treatment

Covariate included	I^2	*tau*2
None	0.78	0.53
Criteria for success (loose or strict)	0.82	0.64
Unit of measure (root or tooth)	0.82	0.64
Geographic location of study (USA, Scandinavian or other countries)	0.78	0.64
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.75	0.40
Duration after treatment (≥4 years or less)	0.80	0.53
Year of publication (before 70's, 1970-1989, 1990-2002)	0.62	0.11

xi) Apical disturbance during root canal treatment

Various studies have investigated the effect of disturbance of the apical tissues during treatment. "Apical disturbance" has however, been defined differently by different researchers. Some (Harty *et al.* 1970, Adenubi & Rule 1976, Nelson 1982) defined it as instrumentation beyond the apical foramen or extrusion of sealer/filling material. Others only considered extrusion of calcium hydroxide (Çalişken & Şen 1996) or sealer (Boggia 1983) into the periapical tissue as apical disturbance. Only 5 studies (Table 3.1.3, page 105) have provided outcome data based on this factor. The pooled success rates for those cases without apical disturbance were higher than those with apical disturbance by 15.6% (loose criteria) and 7.9% (strict criteria), respectively (Table 3.1.25). No further meta-analyses were carried out due to the difference in definition between studies.

Table 3.1.25 Weighted pooled success rates (SR) by apical disturbance

Factor/categories	*Total no. of studies	Strict radiographic criteria			Loose radiographic criteria		
		No. of studies	No. of units	§Weighted pooled SR (%)	No. of studies	No. of units	§Weighted pooled SR (%)
Apical disturbance							
No	4	3	1114	87.0 (82.4, 91.5)	3	1168	88.2(78.9, 97.5)
Yes	5	3	1043	79.1 (65.5, 92.8)	3	173	72.6 (50.3, 94.9)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

xii) Acute exacerbation during treatment

None of the studies reviewed had presented outcome data by this factor (Table 3.1.3, page 105).

xiii) Number of treatment visits

Twenty-five studies had carried out all treatments over multiple visits, whilst in four studies all treatment was completed in one visit. In ten studies, the treatment had been completed in either one or multiple visits, whereas the remainder (22 studies) did not provide this information. Outcome data related to this factor could be extracted from thirty-four studies (Table 3.1.26). The pooled success rates for single-visit treatment were 4% higher (loose criteria) and 0.2% lower (strict criteria) than the success rates for multiple-visit treatment (Table 3.1.26).

Table 3.1.26 Weighted pooled success rates (SR) by number of treatment visits

		Strict radiographic criteria			Loose radiographic criteria		
categories	*Total no. of studies	No. of studies	No. of units	§Weighted pooled SR (%)	No. of studies	No. of units	§Weighted pooled SR (%)
Single	11	6	1077	77.2 (63.8, 90.6)	7 (6)**	538	89.5 (86.8, 92.1)
Multiple	30	18	8373	77.4 (69.3, 85.5)	19	7361	85.5 (80.7, 90.2)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
** Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% success rates by the respective factor under investigation had been excluded.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

Meta-analysis was initially carried out by incorporating all the seven studies which provided success rates by number of visits. No significant difference in the odds of success (OR = 1.16, 95% CI 0.82, 1.63) was found and the heterogeneity was not significant (Table 3.1.27a).

Table 3.1.27a–c Summary of meta-analyses for the effects of treatment visits on success rates of primary root canal treatment

Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity X^2 value	Heterogeneity *P* value
a) Single vs Multiple (7 studies)	7	1.16	0.82, 1.64	4.43	0.619
b) Single vs Multiple (3 randomized controlled trials)	3	1.89	0.99, 3.63	0.027	0.986
c) Single vs Multiple (3 RCTs after excluding cases without pa lesion or not dressed with $Ca(OH)_2$ in multiple visit group)	3	1.35	0.63, 2.88	1.88	0.391

The analysis was repeated after excluding the observational studies, the odds of success for single visit treatment were higher than those for multiple visit treatment (OR = 1.89; 95% CI 0.99, 3.63) and the difference was borderline significant (Table 3.1.27b). However, in one trial (Trope *et al.* 1999), some of the teeth were not associated with pre-operative periapical lesions and some cases treated over multiple visits had not been dressed with an inter-appointment calcium hydroxide dressing (the main biological purpose of multiple visit treatment). After eliminating such cases, the estimated pooled odds ratio decreased to a statistically insignificant level (OR = 1.35, 95% CI 0.63, 2.88) (Table 3.1.27c, page 125). Meta-regression analysis was not performed as the heterogeneity was not significant.

3.1.4.3 Post-operative (root canal treatment) factors

i) Quality of coronal restoration after root canal treatment

Previous studies had categorised the quality of restorations in a variety of ways: for example, restored vs unrestored; satisfactory vs unsatisfactory; or permanent vs temporary. Eight of the 63 studies (Table 3.1.3, page 105) had presented outcome data based on quality of coronal restoration after treatment. The pooled success rates for teeth with "satisfactory" restorations were higher than those teeth with "unsatisfactory" restorations by 10% and 18%, based on loose or strict criteria, respectively (Table 3.1.28a).

Table 3.1.28a&b Weighted pooled success rates (SR) by post-operative restorative status of the tooth

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	*Total no. of studies	No. of studies	No. of units	§ Weighted pooled SR (%)	No. of studies	No. of units	§ Weighted pooled SR (%)
a) Quality of coronal restoration at recall							
Unsatisfactory	6	4	402	60.4 (53.8, 67.1)	2	601	75.6 (56.3, 95.0)
Satisfactory	8	6	763	77.9 (69.7, 86.1)	3	763	85.1 (69.2, 100)
b) Treated tooth being used as abutment for prosthesis							
Yes	1	-	-	-	1	11	45.5 (30.5,60.5)
No	1	-	-	-	1	74	79.7 (75.0,84.4)

*Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
§ Weighted pooled success rates were estimated using random effects meta-analysis (Where there was only one study, its reported success rate and confidence intervals were presented).

Meta-analysis (Table 3.1.29) incorporating seven studies providing success rates by quality of coronal restoration showed that the odds of success (OR = 1.82; 95% CI 1.48, 2.25) were significantly higher in teeth with satisfactory restorations than teeth with unsatisfactory restorations.

Table 3.1.29 Summary of meta-analyses for the effects of quality of coronal restoration on success rates of primary root canal treatment

Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity X^2 value	Heterogeneity *P* value
Satisfactory vs Unsatisfactory	7	1.82	1.48, 2.25	11.87	0.065

The heterogeneity 11.9 [6df] was significant at the 10% level (Table 3.1.29) and could be partly explained by the "year of publication" (Table 3.1.30 – Overleaf).

Table 3.1.30 Meta-regression analyses to account for heterogeneity in analysing the effects of coronal restoration on the success rate of primary root canal treatment

Covariate included	I^2	*tau*2
None	0.50	0.09
Criteria for success (loose or strict)	0.57	0.12
Unit of measure (root or tooth)	Insufficient data	
Geographic location of study (USA, Scandinavian or other countries)	0.54	0.11
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.54	0.11
Duration after treatment (≥4 years or less)	0.53	0.11
Year of publication (before 70's, 1970-1989, 1990-2002)	0.41	0.07

ii) Use as abutment for prosthesis

The data for this factor from a single study (Matsumoto *et al*. 1987) is presented in table 3.1.28b (page 126). No further analysis was carried out due to insufficient data.

3.1.5 Summary of results

The estimated weighted pooled success rates (absence of clinical or radiographic signs of apical periodontitis) of treatments completed at least one year previously, ranged between 68% and 85% when strict criteria were used. The reported success rates have failed to show a consistent trend of improve over the last four or five decades.

Four reported factors were identified as having a significant effect on the outcome of root canal treatment. These included: (1) presence of periapical lesion; (2) apical extent of root filling; (3) quality of root filling; and (4) post-treatment restorative status. The relative strength of effect of each factor and the potential interactions between them could not be precisely determined because of lack of sufficient data. The quality of evidence for treatment factors affecting primary root canal treatment outcome is sub-optimal; there was substantial variation in the study designs. It would be desirable to standardise aspects of study design, data recording and presentation format of outcome data in the much needed future primary root canal treatment outcome studies.

3.2 Meta-analysis of previous data on success rates of secondary root canal treatment based on absence of apical periodontitis as the outcome measure

The results of the systematic review and meta-analysis were combined and have been accepted for publication (Ng *et al.* 2008) in the International Endodontic Journal (Appendix VIII).

3.2.1 Search results, study selection and data extraction

The meta-analysis for secondary root canal treatment included papers published up to December 2006. In total, 40 articles that had reported the outcome of secondary root canal treatment were identified and 21 were excluded for various reasons (recorded in Table 3.2.1). Some papers presented different parts of the same study; therefore their data were combined for analyses: (1) Bergenholtz *et al*. (1979a) & Bergenholtz *et al*. (1979b); (2) Molven & Halse (1988) & Fristad *et al*. (2004).

Each reviewer had entered 185 data points per selected study. Discrepancy was found in 16 of 3330 data points, with 99.5% inter-reviewer agreement.

Table 3.2.1 Reasons for exclusion of the 21 articles

Article	Excluded because following condition not met
1. Puterbaugh (1926)	Overall success rate could not be calculated
2. Rhein *et al*. (1926)	At least 6-month post-operative review
3. Appleton (1932)	At least 6-month post-operative review, same data set as Rhein *et al*. (1926)
4. Buchbinder (1936)	Overall success rate could not be calculated
5. Strindberg (1956)	No stratified data for re-treatment cases
6. Frostell (1963)	No stratified data for re-treatment cases
7. Ingle *et al*. (1965)	No stratified data for re-treatment cases
8. Storms (1969)	Only 4 cases
9. Heling & Kischinovsky (1979)	Only 6 teeth
10. Kerekes & Tronstad (1979)	Overall success rate could not be calculated
11. Cheung (1993)	Not a clinical study
12. Gutknecht *et al.* (1996)	No stratified data for re-treatment cases
13. Hepworth & Friedman (1997)	Not a clinical study
14. Kvist & Reit (1999)	Overall success rate could not be calculated
15. Kvist & Reit (2000)	Not measuring clinical/radiographic success
16. Fava (2001)	Not a clinical study
17. Hoen & Pink (2002)	Not measuring clinical/radiographic success
18. Main *et al*. (2004)	Overall success rate could not be calculated (only considered healing of lesions at the perforation site)
19. Marending *et al*. (2005)	No stratified data for re-treatment cases
20. Spili *et al*. (2005)	No stratified data for re-treatment cases
21. De Quadros *et al*. (2005)	No stratified data for re-treatment cases

3.2.2 Methodological characteristics of selected studies

The 17 selected studies were published between 1961 and 2005 (Table 3.2.2 – Overleaf); none were published in 2006. Most were retrospective studies and only five were prospective cohort studies, of which one (Danin *et al.* 2004) was a randomized controlled trial comparing the outcome of surgical and non-surgical re-treatment of teeth with failed primary root canal treatment. The recall rates (percentage of patients attending for follow-up after treatment) were reported by 16/17 studies and ranged from 20% to 100% with a median of 73.5%. Either root (n=7) or tooth (n=10) was used as the unit of outcome assessment. The sample size ranged from 18 to 452 teeth and 76 to 612 roots.

The treatment outcome was determined rarely by radiographic examination alone (3 studies) and mostly in combination with clinical findings (14 studies) (Table 3.2.2). Most studies (n=14) used strict criteria (complete resolution of periapical lesion at recall) for determination of success. Only 8 studies followed up all the cases for at least 4 years (Table 3.2.2).

For the radiographic assessment of the outcome of treatment, 13 studies (Table 3.2.2) employed at least 2 observers to carry out the assessment. Observer(s) were calibrated prior to evaluation of radiographs in 9 studies and intra- or inter-observer reliability tests were also carried out in 9 studies (Table 3.2.2); only in two of these 9 studies used both of these conditions not met.

The statistical methods used for analysing the association between potential influencing factors and treatment outcome were the chi-square test (10 studies), logistic regression models (3 studies), Mann-Whitney U test (1 study), and logistic regression models using generalised estimating equations (1 study) (Table 3.2.2). Two studies did not analyse the data statistically or did not present such information.

Table 3.2.2 Characteristics of selected studies

Study ID	Authors	Geographic location	[1]Operator	[2]Study design	Recall rate (%)	Sample size (units)	[3]Unit of assessment	[4]Assessment of success	[5]Radiographic criteria of success	≥4 year after treatment	≥ 2 radiographic observers	Calibration	Reliability test	[6]Statistical analysis
1	Grahnén & Hansson (1961)	Sweden	UG	R	64	502	Ro	C&R	S	✓	✓	-	-	.
2	Engström *et al*. (1964)	Sweden	UG	R	72	153	T	C&R	L	✓	✓	-	-	X^2
3	Selden (1974)	USA	Sp	R	20	52	T	C&R	L	-	-	-	-	X^2
4	Bergenholtz *et al*. (1979a&b)	Sweden	UG	R	66	556	Ro	C&R	S	-	✓	-	✓	.
5	Pekruhn (1986)	Saudi Arabia	Sp	R	81	36	T	C&R	S	-	-	-	-	X^2
6	Molven & Halse (1988) & Fristad *et al*. (2004)	Norway	UG	R	50	226	Ro	Ra	S	✓	✓	✓	✓	X^2
7	Allen *et al*. (1989)	USA	-	R	53	315	T	C&R	S	-	-	✓	-	X^2
8	Sjögren *et al*. (1990)	Sweden	UG	R	46	267	Ro	C&R	S	✓	✓	✓	✓	LR
9	Van Nieuwenhuysen *et al*. (1994)	Belgium	-	R	-	612	Ro	C&R	S	-	✓	✓	✓	X^2
10	Friedman *et al*. (1995)	[7]Canada	Sp	C	78	128	T	C&R	S	-	-	-	-	X^2
11	Danin *et al*. (1996)	Sweden	Sp	RCT	100	18	T	Ra	L	-	✓	✓	✓	X^2
12	Sundqvist *et al*. (1998)	Sweden	UG	C	93	50	T	C&R	S	✓	✓	-	-	X^2
13	Chugal *et al*. (2001)	USA	PG	R	75	85	Ro	Ra	S	✓	✓	-	-	LR
14	Hoskinson *et al*. (2002)	UK	Sp	R	78	76	Ro	C&R	S	✓	✓	✓	✓	GEE
15	Farzaneh *et al*. (2004b)	Canada	Sp	C	22	103	T	C&R	S	-	✓	✓	✓	LR
16	Gorni & Gagliani (2004)	Italy	PG	C	94	452	T	C&R	S	✓	✓	✓	✓	M-W
17	Çalişkan (2005)	Turkey	Sp	R	96	86	T	C&R	S	-	✓	✓	✓	X^2

"-" = Missing information;
[1]UG = Undergraduate students, PG = postgraduate students, Sp = Specialist Endodontists;
[2]R = Retrospective study, C = Prospective cohort study, RCT = Randomized controlled trial;
[3]T = Teeth, Ro = Root;
[4]C&R = Combined clinical and radiographic examination, Ra = Radiographic examination only;
[5]S = Strict criteria, L = Loose criteria;
[6]LR = single level logistic regression, GEE = Generalized Estimating Equations, X^2 = Chi square test, M-W = Mann-Whitney U test.
[7]The secondary root canal treatment were carried in Germany, Israel or USA by 3 different operators

3.2.3 Success rates by study characteristics

i) Assessment of outcome and criteria for success

The reported success rates in individual studies ranged from 28% to 90% with a median of 79%. When stratifying the data by "strict" or "loose" criteria, the ranges were 62% to 90% based on strict criteria and 28% to 93% based on loose criteria. The pooled weighted success rate from data based on "strict" criteria (data available from 14 studies) (76.7% [95% CI 73.6%, 89.6%]) (Figure 3.2.1) was similar to that from data based on "loose" criteria (data available from 8 studies) (77.2%, [95% CI 61.1%, 88.1%]) (Figure 3.2.2, page 132). Some studies provided outcome data by both criteria. One study (Danin *et al*. 1996) with a small sample size (n=18) appeared to be an outlier, the pooled success rate by "loose" criteria increased to 82.7% (95% CI 76.5%, 88.9%) after excluding this study (Figure 3.2.3, page 132).

Figure 3.2.1 Probability of success after secondary root canal treatment based on strict radiographic criteria

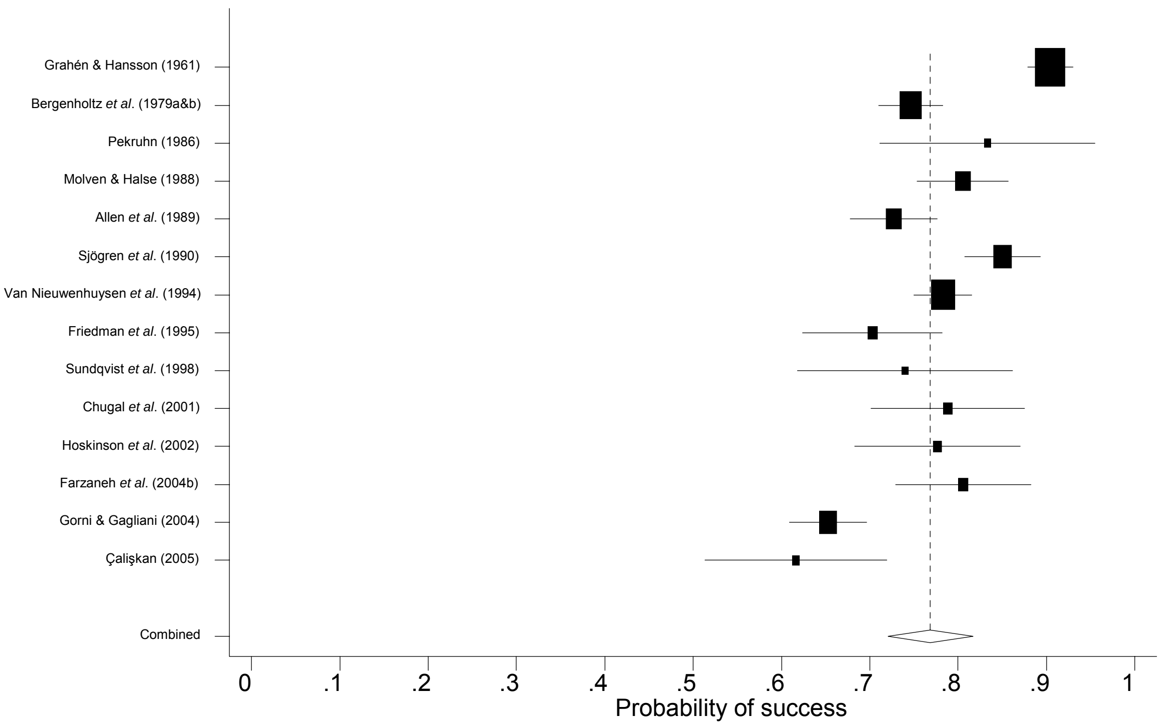


Figure 3.2.2 Probability of success after secondary root canal treatment based on loose criteria

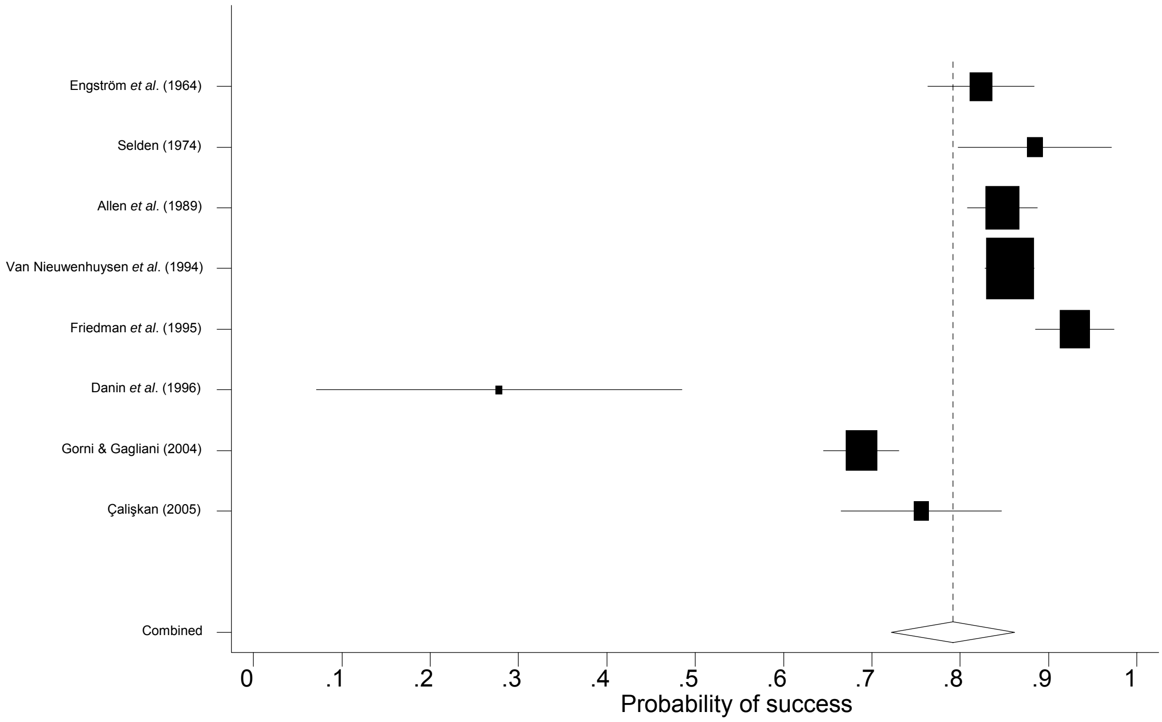
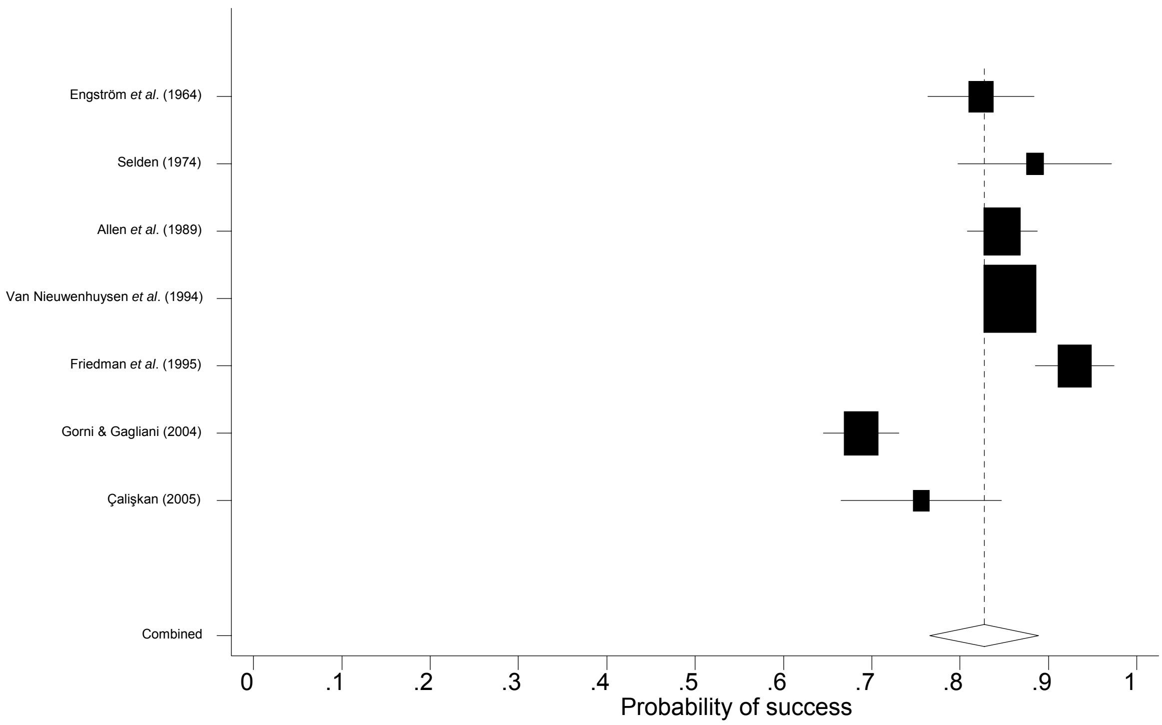


Figure 3.2.3 Probability of success after secondary root canal treatment based on loosed criteria after excluding Danin *et al*. (1996)



For the data based on strict criteria, the pooled success rates by the method of assessment (radiographic & clinical examination versus radiographic examination alone) were similar (Table 3.2.3 – Overleaf). On the other hand, when using loose criteria for determination of success, there was a substantial difference in the pooled success rate based on radiographic & clinical examination (83%) compared with that based on radiographic examination alone (28%) (Table 3.2.3).This is probably accounted for by the fact that only one study had contributed data to the latter category.

ii) Duration of follow-up after treatment completion

Most studies did not standardize duration of review after treatment which ranged from 6 months to 20 years. Attempts to pool data on success rates by different follow-up durations were confounded by either absence of data or the relatively small number of studies in most groups; meaningful comparisons could not, therefore, be made (Table 3.2.3).

Table 3.2.3 Estimated success rates by study characteristics

		Strict radiographic criteria			Loose radiographic criteria		
Factor / categories	***No. of studies Identified**	**No. of studies**	**No. of units**	****Weighted pooled success rate (%)**	**No. of studies**	**No. of units**	****Weighted pooled success rate (%)**
Outcome measure used				**76.7**			**77.2**
Radiographic	3	2	311	80.1 (75.6, 84.5)	1	18	27.8 (7.1, 48.5)
Clinical + Radiographic	14	12	3183	76.4 (70.9, 81.8)	7	1798	82.7 (76.5, 88.9)
Duration after treatment (months)							
6	1	0	-	-	1	155	94.2 (89.3, 97.3)
12	2	1	36	83.3 (67.1, 93.6)	1	18	27.8 (9.7, 53.5)
24	2	2	1008	70.0 (60.9, 79.2)	0	-	-
36	0	0	-	-	0	-	-
48	7	6	1082	85.5 (80.8, 90.1)	1	153	82.4 (75.4, 88.0)
> 48	1	1	226	80.5 (74.8, 85.5)	0	-	-
Year of publication							
1960s	2	1	502	90.4 (87.9, 93.0)	1	153	82.4 (76.3, 88.4)
1970s	2	1	556	74.6 (71.0, 78.3)	1	52	88.5 (79.8, 97.1)
1980s	3	3	577	77.8 (71.3, 84.3)	1	315	84.8 (80.8, 88.7)
1990s	5	4	1057	77.9 (72.0, 83.9)	3	758	76.1 (62.0, 90.1)
2000s	5	5	802	72.7 (64.9, 80.5)	2	538	70.0 (66.2, 73.9)
Geographic location of study* **							
N. American countries	5	4	503	74.7 (71.4, 78.1)	2	367	85.4 (81.8, 89.0)
Scandinavian countries	7	5	1601	81.5 (74.3, 88.7)	2	171	56.0 (2.5, 109.5)
Other countries	5	5	1390	72.9 (65.0, 80.9)	4	1278	80.9 (70.4, 91.5)
Qualification of operators							
Undergraduate students	6	5	1601	81.5 (74.3, 88.7)	1	153	81.0 (76.3, 88.4)
Postgraduate students	2	2	188	79.8 (74.1, 85.6)	0	-	-
Specialist	7	5	778	70.8 (64.0, 77.6)	5	736	73.2 (58.7, 87.7)

* Total number of the studies identified for the respective study characteristic is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria;
** When data were available from only one study for a given factor, the success rate reported by that individual study is presented in this table;
*** N. American countries = USA, Canada; Scandinavian countries = Norway, Sweden; Other countries = UK, Belgium, Italy, Saudi Arabia, Turkey.

iii) Year of publication

The data for outcomes stratified by decades are presented in Table 3.2.3. The pooled success rates for treatments carried out in the “2000’s” appeared to be the lowest ($P < 0.05$) regardless of whether “Strict” or “Loose” outcome criteria were used (Table 3.2.3, page 133). There were no detectable uniform trends of improvement in success rates over the years but outcome data were only available from one study for earlier years.

iv) Geographic location of study

About 40% of the studies were carried out in Scandinavian countries (7 studies, Sweden/Norway) and the rest were carried out in North American (USA/Canada) (5 studies) or other countries (5 studies): UK (1), Belgium (1), Italy (1), Saudi Arabia (1), and Turkey (1). In one study (Friedman *et al.* 1995), the treatments were carried out in USA, Germany or Israel (Table 3.2.2, 130). Based on “loose” criteria, the pooled weighted estimate of success rate of treatment carried out in Scandinavian countries (56%) was much lower than in North American (85%) and other (81%) countries. In marked contrast, the pooled estimate of success rate from outcome data based on strict criteria from the Scandinavian countries (82%) was higher than that from the North American countries (75%) (Table 3.2.3). Meta-regression analyses revealed that the geographic location of study did not have a significant influence on the success rates for teeth with ($P = 0.1$) or without ($P = 0.2$) pre-operative periapical lesion.

v) Qualification of operators (Undergraduate, postgraduate, specialist)

None of the reviewed studies had compared the outcome of secondary root canal treatment by qualification of operators. The reviewed studies mostly classified operator qualification as: undergraduate students (6 studies), postgraduate students (2 studies) or specialists (7 studies) (Table 3.2.2). The operators in the other two studies (Allen *et al.* 1989, Van Nieuwenhuysen *et al.* 1994) were a mixed group of dentists (undergraduate & postgraduate students, specialists) and a single dentist, respectively. From the pooled data, treatment carried out by specialists gave the lowest estimate of success, regardless of use of “strict” or “loose” criteria (Table 3.2.3). Meta-regression analysis, however, revealed that “qualification of operator” had no significant influence on the outcome of secondary treatment on teeth with ($P = 0.6$) or without ($P = 0.2$) pre-operative lesion. The currently available data did not allow further stratified analyses by case complexity, thus the results should be interpreted with caution.

3.2.4 Success rates by clinical factors

Different studies have evaluated the influence of a range of different prognostic factors on outcome but the influence of the combination of factors reported varies (Table 3.2.4, page 136). Attempts to synthesise the effect of individual factors called for the pooling of various equivalent data subsets from these studies. Two approaches were used to analyse the effect of individual factors on success rates, these included the calculation of: (1) Weighted pooled success rate by each factor; and (2) Weighted effect (expressed as weighted pooled odds ratio) of each factor on success rate. Considering only three studies provided stratified data by clinical factors based on loose outcome criteria, *the quantitative analyses were restricted to data based on strict criteria*. The factors were classified into three groups: general and pre-operative factors, intra-operative factors and post-operative restorative factors.

3.2.4.1 Pre-operative factors

i) Gender

Success rate by gender could only be obtained from one study (Hoskinson *et al*. 2002) (Table 3.2.5a, page 137). The success rates for female patients were 44% higher than those for male patients. This result should be interpreted with caution because of the small sample size and substantially smaller number of male than female patients who had received secondary root canal treatment in their study. Further, all the teeth from the male patients were associated with a pre-operative periapical lesion whilst 70% of the teeth in female patients were associated with a pre-operative lesion.

ii) Age

Outcome data related to age was only provided by one study (Hoskinson *et al*. 1990) (Table 3.2.5b, page 137); it showed that treatments carried out in patients within the age band 25-50 years had 4% higher chance of success than those carried out in older patients (>50 years). The results should again be interpreted with caution because of the small sample size.

iii) General medical health

None of the selected studies provided outcome data by this factor, therefore no quantitative analysis was possible.

iii) Tooth type

Only two studies (Bergenholtz 1979a&b, Sjögren *et al.* 1990) had presented outcome data by tooth type (maxillary incisor & canine, maxillary premolar, maxillary molar, mandibular incisor & canine, mandibular premolar, mandibular molar). The weighted pooled success rates for mandibular molar teeth were the highest followed by those for mandibular premolar teeth, then maxillary premolar and molars, and lastly incisors/canines (Table 3.2.5d, page 137).

Table 3.2.4 Clinical prognostic factors reported by selected studies

Study ID	Author (Year)	Gender	Age	Health	Tooth type	Periapical status	Size of periapical lesion	Time interval before 2^oRCT	Pre-operative canal content	Pre-operative perforation	Pre-operative obstruction	Quality of pre-existing RF	Rubber dam isolation	Apical size of canal preparation	Taper of canal preparation	Separation of instrument	Irrigant	Medicament	Culture test	RF material & technique	Sealer	Apical extent of RF	Quality of RF	No. of treatment visits	Restoration after 2^oRCT
1	Grahnén & Hansson (1961)					✓											✓	✓		✓		✓		✓	
2	Engström *et al*. (1964)					✓	✓				☑						✓	✓	✓	✓		☑		✓	
3	Selden (1974)				☑	✓	✓																		
4	Bergenholtz *et al*. (1979a&b)				✓	✓	✓	✓					✓							✓		✓			
5	Pekruhn (1986)				☑								✓				✓	✓		✓	✓			✓	
6	Molven & Halse (1988)					✓														✓				✓	
7	Allen *et al*. (1989)				☑			☑	☑											✓					☑
8	Sjögren *et al*. (1990)	☑	☑		✓	✓	✓				☑		✓				✓		✓	✓		✓	✓	✓	☑
9	Van Nieuwenhuysen *et al*. (1994)	☑	☑				☑						☑				✓			✓	✓	☑	☑	☑	
10	Friedman *et al*. (1995)					✓											✓	✓		✓	✓	☑			☑
11	Danin *et al*. (1996)					✓	✓					✓	✓				✓	✓		✓				✓	
12	Sundqvist *et al*. (1998)					✓	☑	✓					✓				✓	✓	✓	✓		☑		✓	
13	Chugal *et al*. (2001)					☑	☑																		
14	Hoskinson *et al*. (2002)	✓	✓			✓	✓						✓	✓	✓		✓			✓	✓	✓	✓	✓	✓
15	Farzaneh *et al*. (2004b)					✓		✓		✓		✓	✓				✓	✓		✓	✓	✓	☑	✓	✓
16	Gorni & Gagliani (2004)					✓			✓	✓	✓						✓	✓		✓					
17	Çalişkan (2005)			✓		✓	✓	✓	✓				✓				✓	✓		✓	✓			✓	
	Total no. of studies with raw data	**1**	**1**	**1**	**2**	**13**	**7**	**4**	**3**	**2**	**1**	**2**	**8**	**1**	**1**	**0**	**12**	**9**	**3**	**15**	**6**	**5**	**2**	**10**	**2**

RF = root filling; 2^oRCT = secondary root canal treatment; ✓ = Raw data available for estimation of pooled success rates or pooled effects of the respective factor
☑ = The effect of the respective factor had been analysed statistically by individual study but raw data was not available for estimation of the pooled effect in this review.

Table 3.2.5a-k Pooled weighted success rates by pre-operative clinical factors based on strict criteria

Factor	No. of studies	No. of cases	[a]Pooled weighted success rate (%)	Study ID (From table 3.2.4)
a) Gender				
Female	1	56	89.2 (78.1, 96.0)	14
Male	1	20	45.0 (23.1, 68.5)	14
b) Age				
25-50 years	1	32	81.3 (63.6, 92.8)	14
> 50 years	1	43	76.7 (61.4, 88.2)	14
c) Patient's health				
Healthy	1	86	61.6 (50.5, 71.9)	17
Unhealthy	No data	-	-	-
d) Tooth type				
Maxillary incisors/canine	2	108	62.6 (14.1, 111.2)	4, 8
Mandibular incisors	2	49	59.1 (33.4, 84.8)	4, 8
Maxillary premolars	2	136	65.0 (31.3, 98.6)	4, 8
Mandibular premolars	2	89	71.8 (27.8, 115.9)	4, 8
Maxillary molars	2	49	68.0 (55.2, 80.9)	4, 8
Mandibular molars	2	70	85.0 (62.9, 107.1)	4, 8
e) Presence of periapical (pa) lesion				
Without Pa lesion	7(9)[b]	1117 1227	93.5 (92.1, 95.0) 93.4 (91.6, 95.1)[d]	[c]1, (2), 4, 6, 8, [d]10, 14-16 when #10 is included
With Pa lesion	10(13)[b]	1145	65.7 (58.6, 72.7)	[c]1,(2),(3),4, 6, 8,10, (11),12, 14-17
f) Size of periapical lesion				
Pa < 5 mm	4(7)[b]	1386	67.3 (51.7, 83.0)	[c](2), 4, 8, (11), 14,17
Pa > 5mm	4(7)[b]	875	41.7 (32.6, 50.8)	[c](2), (3), 4, 8, (11), 14,17
g) Time interval between previous treatment and re-treatment				
≤ 1 year	1	17	70.6 (44.0, 89.7)	15
> 1 year	4	452	66.2 (28.8, 83.7)	4, 12, 15, 17
h) Pre-existing canal content				
Gutta-percha	1	75	64.0 (52.1, 74.8)	17
Separated instrument	1	61	95.1 (86.3, 99.0)	16
i) Pre-existing perforation				
No	2	561	72.9 (40.3, 105.6)	15, 16
Yes	2	80	41.2 (30.5, 52.0)	15, 16
j) Pre-existing canal obstruction				
Calcification or presence of apical stop	1	103	66.0 (56.0, 75.1)	16
No obstruction	1	349	65.0 (59.8, 70.0)	16
k) Quality of pre-existing root fillings				
Satisfactory	1(2)[b]	19	68.4 (43.4, 87.4)	[c](11), 15
Unsatisfactory	1(2)[b]	80	87.5 (78.2 93.8)	[c](11), 15

[a] Weighted pooled success rates were estimated using the random effect model (where there was only one study, its reported success rate was presented)
[b] Number in bracket was the total number of studies using loose or strict radiographic criteria for determination of success.
[c] Study in bracket was not included in the estimation of pooled success rate because its outcome data for the given factor was based on loose radiographic criteria.
[d] Un-weighted pooled success rate was presented because 100% success rate for the associated category was reported by the respective study.

iv) Periapical status

Stratified outcome data were provided by thirteen studies (Table 3.2.4, page 136). The weighted pooled success rate for teeth without periapical lesion was 28% higher than that for those with periapical lesion pre-operatively (Table 3.2.5e).

Of the above 13 studies, 8 (Grahnén & Hansson 1961, Engström *et al*. 1964, Bergenholtz 1979a&b, Molven & Halse 1988, Sjögren *et al*. 1990, Hoskinson *et al*. 2002, Gorni & Gagliani 2004, Farzaneh *et al*. 2004b) provided stratified outcome data by both teeth with and without periapical lesion enabling comparison by meta-analysis. It was evident that teeth without periapical lesion had 6.32 (95% CI 4.04, 9.90) times higher odds of success than teeth with periapical lesions (Table 3.2.6a – Overleaf). The heterogeneity 16.3 [7 df] was substantial (Table 3.2.6a) and could be partly explained by the "decade of publication" and "duration after treatment" when investigated using meta-regression models (Appendix IX).

Table 3.2.6 Summary of meta-analyses for the effects of pre-operative periapical status on success rates of secondary root canal treatment

Comparisons	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
a) Effects of presence of pre-operative periapical lesion	**8**				
Present		1	-	-	-
Absent		6.32	4.04, 9.90	16.3	0.022
b) Effects of size of pre-operative lesion	**6**				
Large radiolucency (≥ 5 mm in diameter)		1	-	-	-
Small radiolucency (< 5 mm in diameter)		2.64	1.67, 4.17	7.0	0.224

v) Size of periapical lesion

Seven studies (Table 3.2.4, page 136) provided outcome data by the size of lesion. By pooling the data for lesion size into < 5 mm or ≥ 5 mm in diameter, the weighted pooled success rate for small lesions was 25% higher than that for large lesions (Table 3.2.5f, page 137). The estimated pooled odds of success for small lesions was significantly higher when compared to the pooled odds of success for large lesions (OR = 2.64; 95% CI 1.67, 4.17) (Table 3.2.6b). Selden (1974) was excluded from the meta-analysis because all the cases with small lesion were successful. Although, the heterogeneity 7.0 (5df, P = 0.224) in the estimate was not significant (Table 3.2.6b), it could partly be explained by the "duration after treatment" (Appendix IX). In addition, the effect of the size of lesion failed to reach the 5% significance level when the covariate "duration after treatment" was entered simultaneously into the meta-analysis regression model.

vi) Time interval between primary and secondary root canal treatment

Farzaneh *et al*. (2004b) provided outcome data by the time-frame for completion of primary and secondary root canal treatment; these were categorised into those completed more than one year prior to secondary root canal treatment or less than this period. Three other studies had only included teeth with primary root canal treatment carried out at least 2 years (Bergenholtz 1979a&b, Çalişkan *et al*. 2005) or 4–5 years (Sundqvist *et al*. 1998) previously. By pooling the data for time interval between primary and secondary root canal treatment into 1 or less years or more than 1 year, the difference in weighted pooled success rates was 5% in favour of those cases with existing root canal treatments of 1 or less year's duration (Table 3.2.5g, page 137). No further meta-analysis was carried out due to insufficient data.

vii) Pre-operative canal content

Stratified outcome data by teeth with pre-operative gutta-percha root fillings or presence of separated instrument had only been presented by Çalişkan (2005) and Gorni & Gagliani (2004), respectively (Table 3.2.5h, page 137). Meta-analysis was not performed due to insufficient data.

viii) Procedural errors in previous canal preparation (primary root canal treatment)

The procedural errors investigated had included: canal perforation, obstruction and "root canal morphology alteration by previous treatment". The latter was defined by Gorni & Gagliani (2004) as presence of transportation, perforation, stripping or internal resorption; although the last condition was not related to previous treatment.

Success rates stratified by pre-existing perforation were provided by 2 studies (Farzaneh *et al*. 2004b, Gorni & Gagliani 2004); the weighted pooled success rate for teeth without pre-operative perforation was 32% higher than that for teeth with pre-operative perforation (Table 3.2.5i).

The stratified success rates by pre-existing canal obstruction were provided by Gorni & Gagliani (2004) and are presented in table 3.2.5j. Meta-analysis was not performed due to insufficient data.

ix) Quality of pre-operative root fillings

Outcome data by this factor had only been provided by Farzaneh *et al*. (2004b) and is presented in table 3.2.5k. They defined adequate pre-operative root fillings as those extending to 0–2 mm from the radiographic apex without any voids. Meta-analysis was not performed due to insufficient data.

3.2.4.2 Intra-operative factors

i) Use of rubber dam isolation during treatment

Eight studies (Table 3.2.7 – Overleaf) reported the routine use of rubber dam during treatment whilst nine studies did not mention the use of rubber dam isolation in their treatment protocol. The pooled estimated success rate of treatment using rubber dam isolation (n=7 studies) was 77.1%, based on strict criteria (Table 3.2.7). There was insufficient data for further analysis.

ii) Apical extent of instrumentation

Only one study (Bergenholtz *et al*. 1979a) had investigated the effect of this factor (Table 3.2.7). It had been dichotomized into "cleaned" and "un-cleaned" apex: A "cleaned" apex had been defined as instrumentation through the apex. The former cases (56%) were associated with significantly lower success rates than the latter cases (88%), regardless of the pre-operative periapical status of teeth (Table 3.2.7). Meta-analysis was not performed due to insufficient data.

Table 3.2.7 Pooled weighted success rates by use of rubber dam and apical extent & size of canal preparation based on strict criteria

Factor	No. of studies	No. of cases	[a]Pooled weighted success rate (%)	Study ID (From table 3.2.4)
Use of rubber dam isolation				
Yes	7(8)[b]	1174	77.1 (71.6, 82.7)	[c]4, 5, 8, (11), 12, 14, 15, 17
No	No data	–	–	–
Instrumentation beyond apex				
Yes (“cleaned” apex)	1	228	55.7 (49.3, 62.1)	4
No (“uncleaned” apex)	1	328	87.8 (84.3, 91.3)	4
Apical size of canal preparation				
≤ ISO size 30	1	58	84.5 (75.2, 93.8)	14
> ISO size 30	1	18	55.6 (32.6, 78.5)	14
Taper of canal preparation				
.05	1	44	79.5 (67.6. 91.5)	14
.10	1	32	75.0 (60.0, 90.0)	14

[a] Weighted pooled success rates were estimated using the random effect model (where there was only one study, its reported success rate was presented)
[b] Number in bracket was the total number of studies using loose or strict radiographic criteria for determination of success.
[c] Study in bracket was not included in the estimation of pooled success rate because its outcome data for the given factor was based on loose radiographic criteria.
[d] Study excluded for estimation of the weighted pooled success rate because the success rate for the associated category was 100% or 0%.

iii) Apical size of canal preparation

The success rate by apical size of canal preparation smaller or larger than ISO 30, was provided by Hoskinson *et al*. (2002); the data showed that the success rate for small (#20-30) apical preparations (85%) was higher than that for large (#35-90) apical preparations (56%) (Table 3.2.7). The effect of size of preparation could not be analysed further due to insufficient data.

iv) Taper of canal preparation

The success rates stratified by taper of canal preparation were provided by Hoskinson *et al*. (2002) and are presented in table 3.2.7. The effect of taper of canal preparation could not be analysed further due to insufficient data.

v) Separation of instrument during secondary root canal treatment

None of the studies selected had stratified outcome data for this factor.

vi) Irrigant

Different types of irrigants have been used singly or in various combinations in the studies reviewed, including solutions of: sodium hypochlorite (10 studies), sulphuric acid (50%) and sodium bicarbonate (Grahnén & Hansson 1961), and combination of sodium hypochlorite, ethylene-diamine-tetra-acetic acid (EDTA) solution and urea peroxide (Van Nieuwenhuysen *et al*. 1994). Five studies did not present this information. The weighted pooled success rates by different irrigants are presented in table 3.2.8 (Overleaf). The effect of type of irrigant could not be analysed further due to insufficient data.

Table 3.2.8 Pooled weighted success rates by type of irrigant and medicament based on strict criteria

Factor	No. of studies	No. of cases	[a]Pooled weighted success rate (%)	Study ID (From table 3.2.4)
Type of irrigant				
NaOCl	8(10)[b]	1198	74.7 (67.6, 81.8)	[c](2), 5, 8, 10, (11), 12, 14-17
H_2SO_4	1	502	90.4 (87.9, 93.0)	1
NaOCl & EDTA	1	612	78.3 (75.0, 81.5)	9
Type of medicament				
$Ca(OH)_2$	5(6)[b]	792	69.1 (63.8, 74.4)	[c]10, (11), 12, 14, 16, 17
Iodine	0(1)[b]	-	-	[c](2)
Creosote	1	502	90.4 (87.9, 93.0)	1
None	1	36	83.3 (71.2, 95.5)	5

[a] Weighted pooled success rates were estimated using the random effect model (where there was only one study, its reported success rate was presented)
[b] Number in bracket was the total number of studies using loose or strict radiographic criteria for determination of success.
[c] Study in bracket was not included in the estimation of pooled success rate because its outcome data for the given factor was based on loose radiographic criteria.
[d] Study excluded for estimation of the weighted pooled success rate because the success rate for the associated category was 100% or 0%.

vii) Medicament

Some studies standardized the type of medicaments used, and included: calcium hydroxide (n=6), creosote (n=1), and iodine (n=1). Sjögren *et al*. (1990) reported the use of calcium hydroxide in most cases but iodine potassium iodide and camphorated phenol were also used instead in some cases. Van Nieuwenhuysen *et al*. (1994) reported the used of paraformaldehyde in the early part of their study, being replaced by calcium hydroxide in the latter part. An inter-appointment medicament was not used by Pekruhn (1986) because all the cases had been completed in one visit. Six studies did not provide this information.

The pooled success rates stratified by type of medicament are presented in table 3.2.8. There were no data on success rates of treatment using iodine, based on strict criteria. Interestingly, the pooled success rate of secondary root canal treatment using $Ca(OH)_2$ (68.2%) was much lower than treatments using creosote (90.4%) as an inter-appointment medicament. Only one study (Grahnén & Hansson 1961) contributed to the data for creosote and the majority (76%) of the roots in this study were not associated with a pre-operative periapical lesion. Meta-analysis was not performed due to insufficient data.

viii) Root canal bacterial culture test results (positive or negative) prior to obturation

Without stratifying the data by pre-operative periapical status, the pooled weighted success rate for teeth with negative culture results was higher than for teeth with positive culture results by 57% (Table 3.2.9a – Overleaf). However, only one study had contributed to the data on positive cultures. For those teeth without a pre-operative periapical lesion (data provided by Engström *et al*. 1964), the success rate for teeth with negative culture results was 9% higher than for those teeth with positive cultures.

However, their outcomes were based on loose criteria and are therefore not presented in table 3.2.9b. For those teeth with pre-operative periapical lesions, the success rate (based on strict criteria reported by Sundqvist *et al*. 1998) for teeth with negative bacterial cultures prior to root filling was 46% higher than that for teeth with positive cultures (Table 3.2.9c).

Table 3.2.9 Pooled weighted success rates by pre-obturation root canal culture results based on strict criteria

Factor	No. of studies	No. of cases	[a]Pooled weighted success rate (%)	Study ID (From table 3.2.4)
a) Teeth with any periapical status				
Negative culture	2(3)[b]	392	84.4 (80.4, 88.4)	[c](2), 8, 12
Positive culture	1(2)[b]	16	27.0 (4.3, 77.7)	[c](2), 12
b) Teeth with no periapical lesion				
Negative culture	0(1)[b]	-	-	[c](2)
Positive culture	0(1)[b]	-	-	[c](2)
c) Teeth with periapical lesion				
Negative culture	1(2)[b]	44	79.5 (67.6, 91.5)	[c](2), 12
Positive culture	1(2)[b]	6	33.3 (4.3, 77.7)	[c](2), 12

[a] Weighted pooled success rates were estimated using random effect model (where there was only one study, its reported success rate was presented)
[b] Number in bracket was the total number of studies using loose or strict radiographic criteria for determination of success.
[c] Study in bracket was not included in the estimation of pooled success rate because its outcome data for the given factor was based on loose radiographic criteria.
[d] Study excluded for estimation of the weighted pooled success rate because the success rate for the associated category was 100% or 0%.

The results of meta-analyses showed the odds of success for teeth (any periapical status) with pre-obturation negative culture were higher than those for teeth with a positive culture (OR = 4.3; 95% CI 0.3, 55.0) but the difference was not statistically significant (Table 3.2.10a). Although the heterogeneity (6.9 [1 df]) was significant (P = 0.009), further meta-regression analysis was not performed because of insufficient data. For those teeth with periapical lesions, the pooled odds ratio estimated using meta-analysis was not statistically significant (OR = 4.8, 95% CI 0.72, 32.2), with substantial heterogeneity 3.4 (df=1, P=0.066) (Table 3.2.10b) but no further meta-regression was performed due to insufficient data. The results of the meta-analyses for this factor should be interpreted with caution because only 2 studies had contributed data for the analyses.

Table 3.2.10 Summary of meta-analyses for the effects of pre-obturation root canal culture results on success rates of secondary root canal treatment

Comparisons	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
a) Teeth with any pre-operative periapical status	**2**				
+ve culture result		1	-	-	-
-ve culture result		4.30	0.34, 54.9	6.9	0.009
b) Teeth with pre-operative periapical lesion	**2**				
+ve culture result		1	-	-	-
-ve culture result		4.81	0.72, 32.23	3.4	0.066

ix) Root filling material and technique

The types of root filling materials reported were gutta-percha used with various types of sealer (n=8) or gutta-percha softened in chloroform (n=7); three studies did not provide such information. The pooled success rate for teeth filled with gutta-percha and sealer was 8% lower than that for those filled with gutta-percha softened in chloroform (Table 3.2.11a).

Table 3.2.11a-d Pooled weighted success rates by factors related to root filling based on strict criteria

Factor	No. of studies	No. of cases	[a]Pooled weighted success rate (%)	Study ID (From table 3.2.4)
a) Root filling material / technique				
Gutta-percha with sealer	8	1808	73.5 (68.5, 78.4)	5, 7, 9, 10, 14–17
Kloropercha	5(7)[b]	1601	81.5 (74.3, 88.7)	[b]1, (2), 4, 6, 8, (11), 12
b) Type of sealer				
Zinc oxide eugenol based	4	1176	75.4 (66.8, 83.9)	5, 9, 14, 15
Glass ionomer based (Ketac Endo®)	1	128	70.3 (62.4, 78.2)	10
Polyvinyl resin based (Diaket®)	1	86	61.6 (51.4, 71.9)	17
c) Apical extent of root filling				
Short-filled	3	229	87.4 (74.2, 100.7)	1, 8, 14
Flush-filled	4	310	80.5 (68.6, 92.4)	1, 8, 14, 15
Long-filled	4	406	63.1 (42.9, 83.4)	1, 4, 8, 14
Short-fill – no pa	2	159	100.0	1, 14
Flush-fill – no pa	2	120	97.2 (94.3, 100.1)	1, 14
Long-fill – no pa	2(3)[d]	179 194	84.0 (78.8, 89.1) 84.0 (78.8, 89.3)[d]	1, 4, [d]14 When #14 included
Short-fill – pa	3	70	78.5 (69.0, 88.0)	1, 8, 14
Flush-fill – pa	3	112	72.2 (64.0, 80.4)	1, 8, 14
Long-fill – pa	4	212	54.2 (30.8, 77.6)	1, 4, 8, 14
d) Quality of root filling				
Satisfactory	2	157	71.8 (64.8, 8.8)	8, 14
Unsatisfactory	1(2)[d]	13 15	30.8 (5.68, 55.9) 26.6 (4.3, 49.0)[d]	8, [d]14 When #14 was included

[a] Weighted pooled success rates were estimated using random effect model (where there was only one study, its reported success rate was presented)
[b] Number in bracket was the total number of studies using loose or strict radiographic criteria for determination of success.
[c] Study in bracket was not included in the estimation of pooled success rate because its outcome data for the given factor was based on loose radiographic criteria.
[d] Study excluded for estimation of the weighted pooled success rate because the success rate for the associated category was 100% or 0%.

Three types of sealer had been used, including: Zinc oxide eugenol-based sealers (4 studies), glass ionomer-based sealer (KetacEndo®, ESPE Gmbh, Seefeld, Germany) (1 study) or resin-based sealer (Diaket®, ESPE Gmbh, Seefeld, Germany) (1 study). Eleven studies did not provide such information (Table 3.2.4, page 130). The pooled success rates for teeth filled with the resin-based sealer (62%) was lower than those obturated with zinc oxide eugenol-based (75%) or glass ionomer-based (70%) sealers (Table 3.2.11b).

Of the eight studies using gutta-percha and sealer, only three studies (Pekruhn 1986, Gorni & Gagliani 2004, Çalişkan *et al*. 2005) standardized the obturation technique. The former two used the warm vertical compaction technique whilst Çalişkan *et al*. (2005) used the cold lateral compaction technique. Four studies (Van Nieuwenhuysen *et al*. 1994, Friedman *et al*. 1995, Hoskinson *et al*. 2002, Farzaneh *et al*. 2004b) did not standardize the root filling technique and one (Allen *et al*. 1989) did not provide such information.

The effects of root filling techniques and materials including the type of sealer were not estimated due to insufficient data.

x) Apical extent of root filling

Four studies had provided the success rate by this factor. The pooled success rates (without stratifying the data by pre-operative periapical status) by apical extent of root fillings in descending order were: short (87%), flush (81%) and long (63%) root fillings (Table 3.2.11c, page 143). Some studies provided the success rates stratified by periapical status and apical extent of root filling. The pooled success rates for long root fillings were the lowest regardless of the periapical status (Table 3.2.11c).

Only three studies presented success rates by all the three extents (short, flush, long) of root fillings for meta-analyses. Teeth with short (OR = 4.11; 95% CI 2.10, 8.07) or flush (OR = 2.36; 95% CI 1.36, 4.10) root fillings had significantly higher success rates than those teeth with long root fillings (Table 3.2.12a). The results of meta-analyses on the data from teeth *with* pre-operative periapical lesions revealed similar trends with lower odds ratios and statistically insignificant findings (Table 3.2.12b). The heterogeneity was not significant, therefore further meta-regression analysis was not performed.

Table 3.2.12a&b Summary of meta-analyses for the effects of apical extent of root filling on success rates of secondary root canal treatment

Comparisons	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
a) Teeth with any pre-operative periapical status	**3**				
Long		1	-	-	-
Flush		2.36	1.36, 4.10	1.4	0.500
Short		4.11	2.10, 8.07	2.5	0.286
b) Teeth with pre-operative lesion	**3**				
Long		1	-	-	-
Flush		1.65	0.86, 3.16	0.39	0.824
Short		1.72	0.81, 3.64	1.17	0.558

xi) Quality of root filling

Of the four studies (Table 3.2.4, page 130) that had analysed this aspect statistically, only two studies provided stratified data by quality of root filling. The pooled success rate for teeth with satisfactory root fillings was 41% higher than for those teeth with unsatisfactory root fillings (Table 3.2.11d). There were, however no successful cases with unsatisfactory root filling in one study (Hoskinson *et al*. 2002), therefore no further meta-analysis was carried out due to insufficient data.

xii) Number of treatment visits

Five studies completed treatment in either one or multiple visits, eight studies carried out treatments over multiple visits only, only one study completed all treatment in one visit, whereas others (3 studies) did not provide this information. The pooled success rate for single-visit treatment was 4.8% higher than the success rate for multiple-visit treatment but only one study had contributed to the data based on strict criteria for single-visit treatment (Table 3.2.13). The pooled effect of number of treatment visits was not estimated due to insufficient data.

Table 3.2.13 Pooled weighted success rates by factors related to number of treatment visits based on strict criteria

Factor	No. of studies	No. of cases	[a]Pooled weighted success rate (%)	Study ID (From table 3.2.4)
Single visit	1(2)[d]	52	83.3 (71.2, 95.5) 86.1 (27.7, 144.4)[d]	5, [d]15 When #15 was included
Multiple visits	7(9)[b]	1461	79.5 (73.2, 85.8)	[c]1, (2), 6, 8, (11), 12, 14, 15, 17

[a] Weighted pooled success rates were estimated using the random effect model (where there was only one study, its reported success rate was presented)
[b] Number in bracket was the total number of studies using loose or strict radiographic criteria for determination of success.
[c] Study in bracket was not included in the estimation of pooled success rate because its outcome data for the given factor was based on loose radiographic criteria.
[d] Study excluded for estimation of the weighted pooled success rate because the success rate for the associated category was 100% or 0%.

3.2.4.3 Post-operative restoration status after secondary root canal treatment

Stratified data by the quality of restoration after treatment were provided by two studies (Hoskinson *et al*. 2002, Farzaneh *et al*. 2004b) (Table 3.2.14) and the pooled success rate for teeth with satisfactory restorations was 24% higher than for those with unsatisfactory restorations (Table 3.2.14).

Table 3.2.14 Pooled weighted success rates by quality of post-operative restoration based on strict criteria

Factor	No. of studies	No. of cases	[a]Pooled weighted success rate (%)	Study ID (From table 3.2.4)
Satisfactory	2	155	84.1 (78.4, 89.9)	14, 15
Unsatisfactory	2	20	60.0 (38.6, 81.5)	14, 15

[a] Weighted pooled success rates were estimated using the random effect model (where there was only one study, its reported success rate was presented)

The effect of quality of coronal restoration (OR = 3.31; 95%CI 1.07, 10.3) was estimated based on the data from these two studies and found to be significant at the 5% level although the confidence interval was wide (Table 3.2.14). The heterogeneity was not significant and no further meta-regression analysis was carried out (Table 3.2.15 – Overleaf).

Table 3.2.15 Summary of meta-analyses for the effects of quality of post-operative restoration on success rates of secondary root canal treatment

Comparisons	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
Unsatisfactory		1	-	-	-
Satisfactory		3.31	1.07, 10.3	0.21	0.647

3.2.5 Summary of results

The pooled estimated success rate for secondary root canal treatment was 77%. The presence of pre-operative periapical lesion, apical extent of root filling and quality of coronal restoration proved to be significant prognostic factors whilst the effects of primary root canal treatment history and secondary root canal treatment protocol were found to have been poorly investigated.

3.3 Meta-analysis of previous data on the survival of teeth after primary or secondary root canal treatment

3.3.1 Search results, study selection and data extraction

The literature search for meta-analysis of probability of tooth survival following primary or secondary root canal treatment extended up to December 2007. Out of the 31 papers identified, 17 were excluded for reasons listed in table 3.3.1.

Table 3.3.1 Reasons for exclusion of the 17 articles

Article	Excluded because following condition ***not*** met
1. Molven (1976)	Tooth survival probability provided
2. Hansen *et al*. (1990)	Tooth survival probability provided
3. Caplan & Weintraub (1997)	Tooth survival probability provided
4. Glazer (2000)	Tooth survival probability provided
5. Mannocci *et al*. (2002)	Tooth survival probability provided
6. Mannocci *et al*. (2005)	Tooth survival probability provided
7. Nagasiri & Chitmongkolsuk (2005)	Tooth survival probability provided
8. Willershausen *et al*. (2005)	Tooth survival probability provided
9. Kolker *et al*. (2006)	Teeth had root canal treatment
10. De Backer *et al*. (2006)	Tooth survival probability provided
11. Wegner *et al*. (2006)	Tooth survival probability provided
12. White *et al*. (2007)	Longitudinal clinical study
13. Ferrari *et al*. (2007)	Tooth survival probability provided
14. Piovesan *et al*. (2007)	Tooth survival probability provided
15. De Backer *et al*. (2007)	Tooth survival probability provided
16. Adolphi *et al*. (2007)	Tooth survival probability provided
17. Miyamoto *et al*. (2007)	Tooth survival probability provided

3.3.2 Characteristics of selected studies

The fourteen studies investigating the survival of teeth after primary or secondary root canal treatment were published between 1993 and 2007 (Table 3.3.2 – Overleaf). The selected studies were designed to address different research questions mostly related to the post-treatment tooth restoration (Table 3.3.2). The majority were retrospective (n=10) and four were prospective cohort studies. The sample size ranged from 50 teeth (Tan *et al*. 2006) to 1,462,936 (Salehrabi & Rotstein 2004) teeth. Two studies (Aquilino & Caplan 2002, Caplan *et al*. 2002) had selected two different cohorts from the original cohort of patients in order to address two different research questions. Furthermore, Caplan *et al*. (2005) also selected a subset of patients from a prior case-control study (Caplan & Weintraub 1997) to investigate the prognostic factors for tooth survival after root canal treatment. All the selected studies had only investigated survival of teeth following after *primary root canal treatment*; with one exception (Stoll *et al*. 2005), in which 13% of the cases had undergone secondary root canal treatment.

The duration of survival after root canal treatment of the tooth ranged from 1 to 11.5 years. Investigation of the prognostic factors for tooth survival after primary or secondary root canal treatment, had involved a number of statistical methods including: X^2 (n=5), Kaplan-Meier (n=4), Cox regression (n=2), construction of life table (n=1); Mantel-Haenszel method (n=1), and generalised estimating equations (n=1) (Table 3.3.2).

Table 3.3.2 Characteristics of and survival rates reported by the selected studies (n=14)

Study	Main research question	[a]Study design	Sample size	[b]RCTx	[c]Statistical method	Survival rate
1. Mackie *et al*. (1993)	Survival of teeth with immature apex after RCTx	P	93 teeth	1^o	L-T	86% (5 yr) 86% (10 yr)
2. Lazarski *et al*. (2001)	Prevalence and effect of crown and qualification of operator on untoward events after 1^oRCTx	R	44,613 cases	1^o	M-H	94.4% (2–6 yr) [mean = 2 yr]
3. Aquilino & Caplan (2002)	Effect of crown placement	R	203 teeth (156 patients) (from a pool of 400 teeth)	1^o	CR	79.3% (10 yr)
4. Caplan *et al*. (2002)	Effect of number of proximal contacts	R	221 teeth (180 patients) (from a pool of 400 teeth)	1^o	CR	75.1% (10 yr)
5. Dammaschke *et al*. (2003)	Over 10 year survival of teeth after RCTx	R	190 teeth (144 patients)	1^o	K-M	87.4% (≥ 10 yr)
6. Alley *et al*. (2004)	Influence of operator	R	350 teeth	1^o	X^2	93.4% (5 yr)
7. Lynch *et al*. (2004)	Effect of type of coronal restoration	R	176 teeth (166 patients)	?	X^2	35% – 92% (1-5 yr) [mean = 3 yr]
8. Salehrabi & Rotstein (2004)	Tooth retention over 8 years after RCTx	R	1,462,936 teeth	1^o	X^2	97.1% (8 yr)
9. Tilashalski *et al*. (2004)	Outcome of endodontic treatment	P	75 teeth – 45 yr or older	1^o	GEE	81% (4 yr)
10. Caplan *et al*. (2005)	8-year survival of teeth with RCTx and teeth without RCTx	C-C (R)	202 matched pairs of teeth; (original pool = 1795 teeth/patients)	1^o	K-M	84.8% (8 yr)
11. Stoll *et al*. (2005)	Prognostic factors for survival of treatment	R	965 teeth	*$1^o/2^o$	K-M	89.4% (10.3 yr)
12. Tan *et al*. (2006)	Survival of cracked teeth after RCTx	P	50 teeth (49 patients)	1^o	K-M	85.5% (2 yr)
13. Chen *et al*. (2007)	Tooth retention and untoward events over 5 years after RCTx	R	1,557,547 teeth	1^o	X^2	93.2% (5 yr)
14. Salvi *et al*. (2007)	Effect of post placement in teeth after RCTx	P	308 teeth (166 patients)	1^o	X^2	93.8% (2.1–11.5 yr [mean 5.3yr])

[a]C-C = case control study; P = prospective study; R = Retrospective study; [b]RCTx = Root canal treatment (1^o = primary; 2^o = secondary; ? = unknown)
[c]L-T = Life table; M-H = Mantel-Haenszel method; CR = Cox regression; K-M = Kaplan-Meier; GEE = Generalised estimating equations
*13% of cases undergone 2^oRCT

3.3.3 Survival rates

Estimation of the pooled survival rate, was achieved by partitioning the data for 2–3, 4–5 and 8–10 years for meta-analyses; the survival rates were: 86.4% (95% CI 74.7%, 98.1%), 93.3% (95% CI 92.0%, 94.4%) and 86.7% (95% CI 81.6%, 91.8%), respectively (Figures 3.3.1–3.3.3).

Figure 3.3.1 Two to three year tooth survival probability after root canal treatment

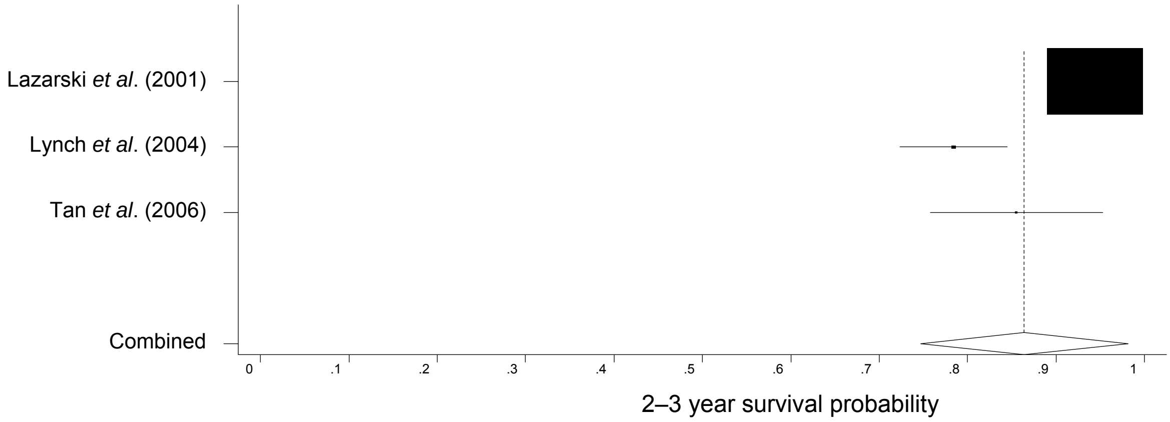


Figure 3.3.2 Four to five year tooth survival probability after root canal treatment

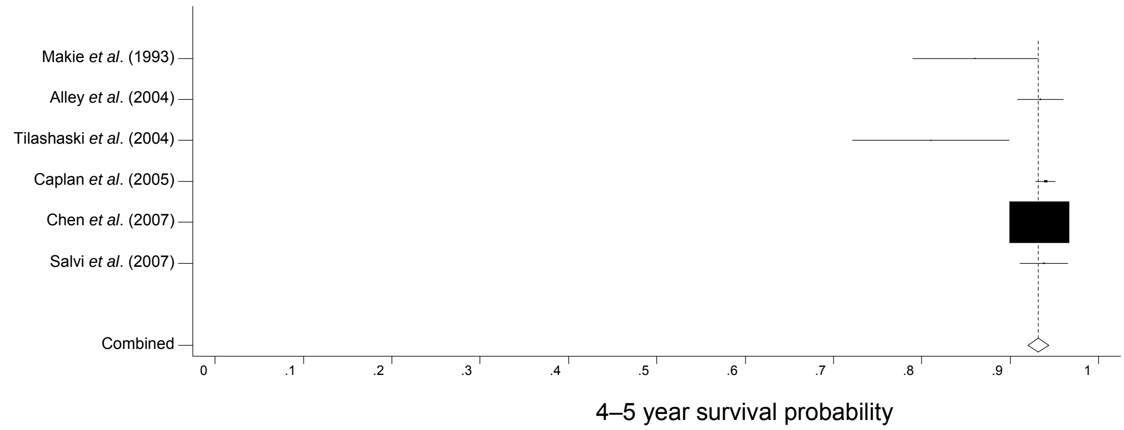
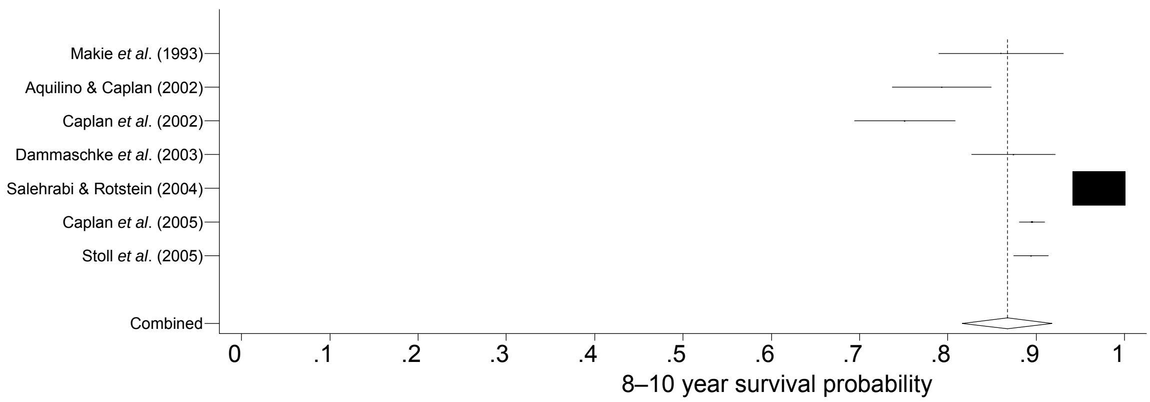


Figure 3.3.3 Eight to ten year tooth survival probability after root canal treatment



3.3.4 Prognostic factors for tooth survival

The prognostic factors investigated may be classified into general patient factors, pre-operative tooth factors, intra-operative factors and post-operative restorative factors (Table 3.3.3). The two most frequently investigated were type and location of the tooth (n=8) followed by type of coronal restoration (n=6).

Table 3.3.3 Prognostic factors investigated in selected studies

Factors	Mackie *et al*. (1993)	Lazarski *et al*. (2001)	Aquilino & Caplan (2002)	Caplan *et al*. (2002)	Dammaschke *et al*. (2003)	Alley *et al*. (2004)	Lynch *et al*. (2004)	Salehrabi & Rotstein (2004)	Tilashalski *et al*. (2004)	Caplan *et al*. (2005) /	Stoll *et al*. (2005)	Tan *et al*. (2006)	Chen *et al*. (2007)	Salvi *et al*. (2007)	Total
Operator		×				✓			×		×				4
Sex		×		☒	☒							×			4
Age		☑	×		×										3
Ethic origin												×			1
Medical condition				×											1
Tooth type & location		✓	✓	✓	☒	?		?		☑		✓	✓	×	8
Pre-operative pain											✓				1
Pulpal status											✓				1
Periapical status			×		✓						✓				3
1°RCT vs 2°RCT				×							×				2
Pre-operative pocket												✓			1
Pre-operative cracks												✓			1
RF extent and quality				×	☑	✓					✓				4
Duration between root filling and restoration			×												1
Proximal contacts			×	✓											2
Type of restoration		?	✓	✓	✓	?	✓	✓						×	6
Type of core				×		?									1
Presence and type of post		✓	×		×	?		☒						×	5
Abutment		✓				×								?	2

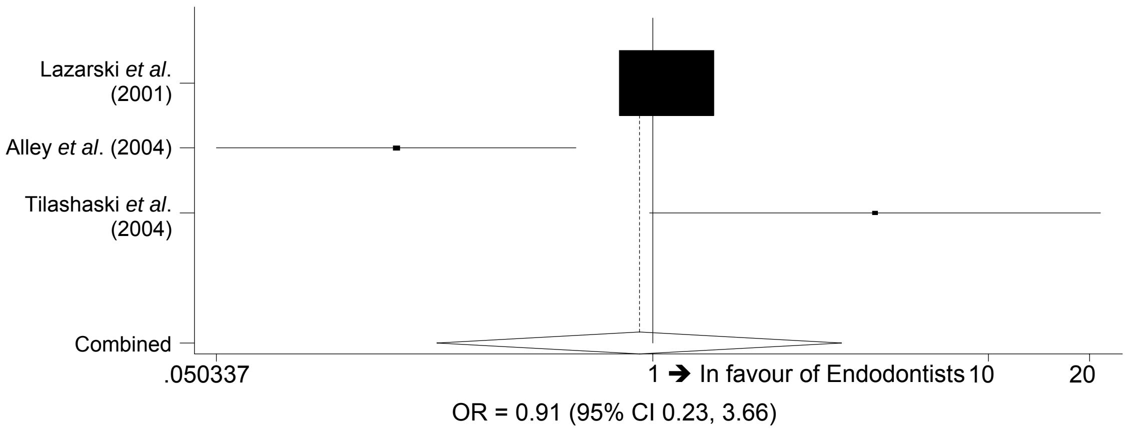
✓ = identified as significant factor and data available; ☑ = significant factor but data not available;
× = identified as insignificant factor and data available; ☒ = insignificant factor but data not available;
? = data available but effect was not investigated; empty box = factor not investigated and data not available.
1°RCT = primary root canal treatment; 2°RCT = secondary root canal treatment; RF = root filling

3.3.4.1 General and pre-operative factors

i) Qualification of operators

Three studies (Larzarski *et al*. 2001, Alley *et al*. 2004, Tilashaski *et al*. 2004) had provided tooth survival data on treatment carried out by generalists and endodontists. More recently, Stoll *et al*. (2005) reported the survival data by qualified dentist (generalist) and dental students. The data from the first three studies were pooled for meta-analysis. It was found that teeth treated by generalists were associated with a slightly lower probability of survival (OR = 0.91; 95% CI 0.23, 3.66) but the difference was not significant (Figure 3.3.4). Although the heterogeneity 12.0 [2df] was substantial (P = 0.003), meta-regression was not performed due to insufficient data.

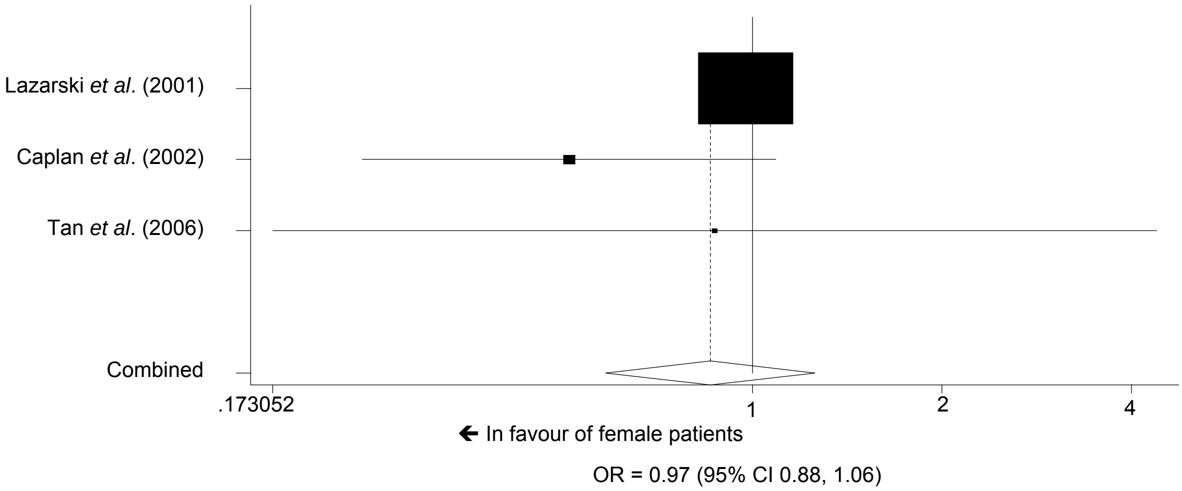
Figure 3.3.4 Comparison of survival of teeth treated by endodontists and non-endodontists



ii) Gender, age, medical status and ethnic origin of patient

The tooth survival probabilities by sex were provided by three studies (Lazarski *et al*. 2001, Caplan *et al*. 2002, Tan *et al*. 2006). Caplan *et al*. (2002) presented both 5-year and 10-year survival rates; the 5-year survival data were used for meta-analysis because the other two studies only followed the cases for up to 6 years. The result showed that male patients were associated with a slightly lower probability of tooth survival after root canal treatment (OR = 0.97; 95%CI 0.88, 1.06) compared with female patients, although the difference was not significant (Figure 3.3.5 – Overleaf). The heterogeneity 2.7 [2df] was also not significant.

Figure 3.3.5 Comparison of survival of teeth by male and female patients



Although three studies (Lazarski *et al*. 2001, Aquilino & Caplan 2002, Dammaschke *et al*. 2003) had investigated the effect of age, only one (Aquilino & Caplan 2002) presented the survival probabilities by this factor. They partitioned age into three bands: 54 years or younger, 55 upto 64 and 65 or older. The corresponding 5-year survival rates were 93% (87%, 98%), 87% (79%, 96%), 82% (72%, 92%), whilst the 10-year survival rates were 82% (74%, 90%), 84% (75%, 93%), 69% (57%, 81%), respectively.

The effect of the patient's medical condition had only been investigated in one study (Caplan *et al*. 2002). The reported 5-year & 10-year tooth survival rates for patients receiving medication for heart disease/hypertension or not were 82% (69%, 95%) & 65% (47%, 80%) and 86% (81%, 91%) & 63% (56%, 70%), respectively.

The association between the patient's ethnic origin and tooth survival after root canal treatment was again only investigated in one study (Tan *et al*. 2006), where all the root treated teeth had identified cracks pre-operatively. They classified the ethnic groups into Chinese, Indian and others; the 2-year tooth survival rates were 83% (72%, 95%), 100% and 100%, respectively.

The effects of the above three factors were not estimated using meta-analysis due to insufficient data.

iii) Location and type of tooth

Eight studies (Lazarski *et al*. 2001, Aquilino & Caplan 2002, Caplan *et al*. 2002, Alley *et al*. 2004, Salehrabi & Rotstein 2004, Tan *et al*. 2006, Chen *et al*. 2007, Salvi *et al*. 2007) presented survival rates of anterior, premolar and molar teeth after root canal treatment. The data from Caplan *et al*. (2002) were excluded because their study cohort was selected from the same patient pool as Aquilino & Caplan (2002). There was no loss of anterior teeth after treatment in the study by Salvi *et al*. (2007), therefore they could not be included in these analyses. In contrast, Tan *et al*. (2006) had not included anterior teeth in their sample.

The results revealed that the survival probability of anterior teeth was higher than that for premolar (OR = 1.29; 95% CI 0.91, 1.84) and molar (OR = 1.29; 0.91, 1.82) teeth, although the differences were not significant (Table 3.3.4). However, premolars were associated with significantly higher survival rates (OR = 1.19; 95% CI 1.01, 1.41) than molars.

In order to include data from more studies, the data from anterior and premolar teeth were pooled into a non-molar category for further analysis. This revealed that non-molar teeth were associated with significantly higher survival probability (OR = 1.26; 95% CI 1.00, 1.58) than molar teeth (Table 3.3.4).

The heterogeneity was substantial for all the above analyses but meta-regression was not carried out due to insufficient data.

Table 3.3.4 Summary of meta-analyses for the effects of tooth type on survival probability of teeth after root canal treatment

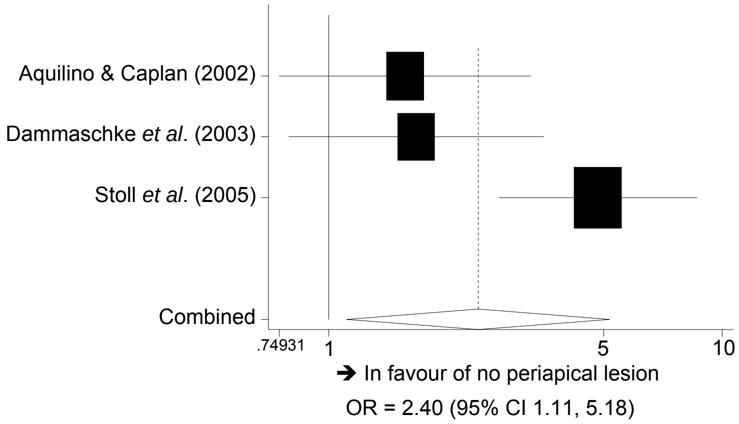
Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
Anterior teeth vs premolars	5	1.29	0.91, 1.84	763.9	<0.001
Anterior teeth vs molars	5	1.28	0.91, 1.82	1058.8	<0.001
Premolars vs molars	7	1.19	1.01, 1.41	245.4	<0.001
Non-molars vs molars	7	1.26	1.00, 1.58	799.8	<0.001

iv) Pulpal and periapical status

Only one study (Stoll *et al*. 2005) had investigated the effect of pre-operative pain and pulpal status on tooth survival. They found vital teeth (81%) or teeth without pre-operative pain (79%) were associated with significantly higher survival rates than non-vital teeth (68%) or teeth with pre-operative pain (67%), respectively.

Three studies (Aquilino & Caplan 2002, Dammaschke *et al*. 2002, Stoll *et al*. 2005) had provided survival probabilities by the presence of pre-operative periapical lesion. Teeth without a periapical lesion were associated with a significantly higher chance of survival than those with a pre-operative lesion (OR = 2.40; 95% CI 1.11, 5.18) (Figure 3.3.6 – Overleaf); with substantial heterogeneity 7.6 [3df]. The study by Stoll *et al*. (2005) had included competing outcomes other than tooth survival such as root canal re-treatment. The meta-analysis was therefore repeated by excluding this study to reveal a smaller and now insignificant influence from this factor (OR = 1.62; 95% CI 0.96, 2.73).

Figure 3.3.6 Comparison of survival of teeth with absence or presence of periapical lesion



v) Presence of crack and pre-operative periodontal pocket

One prospective study (Tan *et al.* 2006) specifically investigated the survival of and the prognostic factors for teeth with cracks prior to primary root canal treatment. The results of their analyses are presented in table 3.3.5 but should be interpreted with caution due to the small sample size.

Table 3.3.5 Results of analyses by Tan *et al*. (2006)

Prognostic factors (Test vs Reference categories)	Odds ratio	95% CI
Location of cracks		
Mesial vs not	1.4	0.4, 5.4
Distal vs not	No loss of teeth with distal cracks	
Buccal vs not	0.9	0.1, 4.3
Palatal or lingual vs not	1.8	0.5, 6.2
Multiplicity of cracks		
Multiple vs single	No loss of teeth with single crack	
Extension of cracks		
Radicular extension vs within crown	2.5	0.6, 8.2
Pre-operative pocket		
Present vs absence	4.9	1.2, 2.0

3.3.4.2 Intra-operative factors

i) Apical extent of root filling

Three studies (Dammaschke *et al.* 2003, Alley *et al.* 2004, Stoll *et al.* 2005) had investigated the effect of apical extent of root filling on the survival of teeth after treatment, however only the latter two presented the survival data. The weighted pooled survival rates for short, flush and long root fillings were estimated (Table 3.3.6 – Overleaf). Teeth with flush root fillings were associated with significantly higher survival probability (OR = 4.70, 95% CI 2.98, 7.41) than teeth with short root fillings. The heterogeneity 1.4 [1 df] (P = 0.2) was not significant.

Table 3.3.6 Pooled estimated survival probabilities by apical extent of root fillings

Extent of root filling	Number of studies	Number of teeth	Weighted pooled survival rate (%)
Short	2	211	80.9 (68.0, 93.9)
Flush	2	837	94.6 (93.0, 96.1)
Long	1 (Data from Alley *et al*. 2004 excluded because no loss of teeth in this category)	117	74.0 (65.6, 82.5) (Results reported by Stoll *et al*. 2005)

ii) Quality of root filling

Only one study (Caplan *et al.* 2002) had investigated this factor. The 5-year and 10-year estimated survival probabilities were: 0.85 (0.80, 0.90) & 0.62 (0.55, 0.69) for teeth without voids in the root filling (n=188 teeth) and 0.86 (0.73, 0.99) & 0.68 (0.51, 0.85) for teeth with voids in root filling (n=28 teeth), respectively. Meta-analysis could not be carried out due to insufficient data.

3.3.4.3 Post-operative restorative factors

i) Type of coronal restoration

Four studies (Lazarski *et al*. 2001, Aquilino & Caplan 2002, Alley *et al*. 2004, Lynch *et al*. 2004) had provided survival data by teeth restored with or without a crown after treatment. Those teeth restored with a crown were associated with significantly higher survival probability (OR = 3.92; 95% CI 3.54, 4.33) than those without a crown after root canal treatment (Table 3.3.7). However, survival data stratified by anterior and posterior teeth were only provided by Lynch *et al*. (2004) therefore subgroup meta-analysis by tooth type was not feasible.

Table 3.3.7 Summary of meta-analyses for the effects of type of restorative status of teeth after treatment

Comparisons (Test vs Reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity	
				X^2 value	*P* value
Restoration with crown (yes vs no)	4	3.92	3.54, 4.33	0.5	0.9
Restoration retained with post (yes vs no)	5	0.89	0.75, 1.05	16.5	0.002
Functioned as abutment (no vs yes)	3	1.70	1.31, 2.20	3.23	0.2
Number of proximal contacts (two vs 1 or 0)	2	3.08	1.78, 5.32	0.99	0.3

Survival data by presence of post were provided by 5 studies (Lazarski *et al*. 2001, Aquilino & Caplan 2002, Dammaschke *et al*. 2003, Alley *et al*. 2004, Salvi *et al*. 2007). There was no significant difference in survival probability (OR = 0.89; 95% CI 0.75, 1.05) between teeth with or without a post retained restoration after root canal treatment (Table 3.3.7). The data heterogeneity was however, substantial.

Meta-analysis of data pooling from three studies (Lazarski *et al*. 2001, Alley *et al*. 2004, Salvi *et al*. 2007) revealed that teeth not functioning as prosthetic abutments were associated with (OR = 1.70; 95% CI 1.31, 2.20) a higher survival probability than those that did.

ii) Number of proximal contacts

Only two studies (Aquiline & Caplan 2002, Alley *et al*. 2004) had provided survival data by the number of proximal contacts. Teeth with both mesial and distal adjacent teeth (2 proximal contacts) were associated with a significantly higher survival probability (OR = 3.08; 95% CI 1.78, 5.32) than those with one or more missing adjacent teeth (Table 3.3.7, page 155).

4.3.5 Summary of results

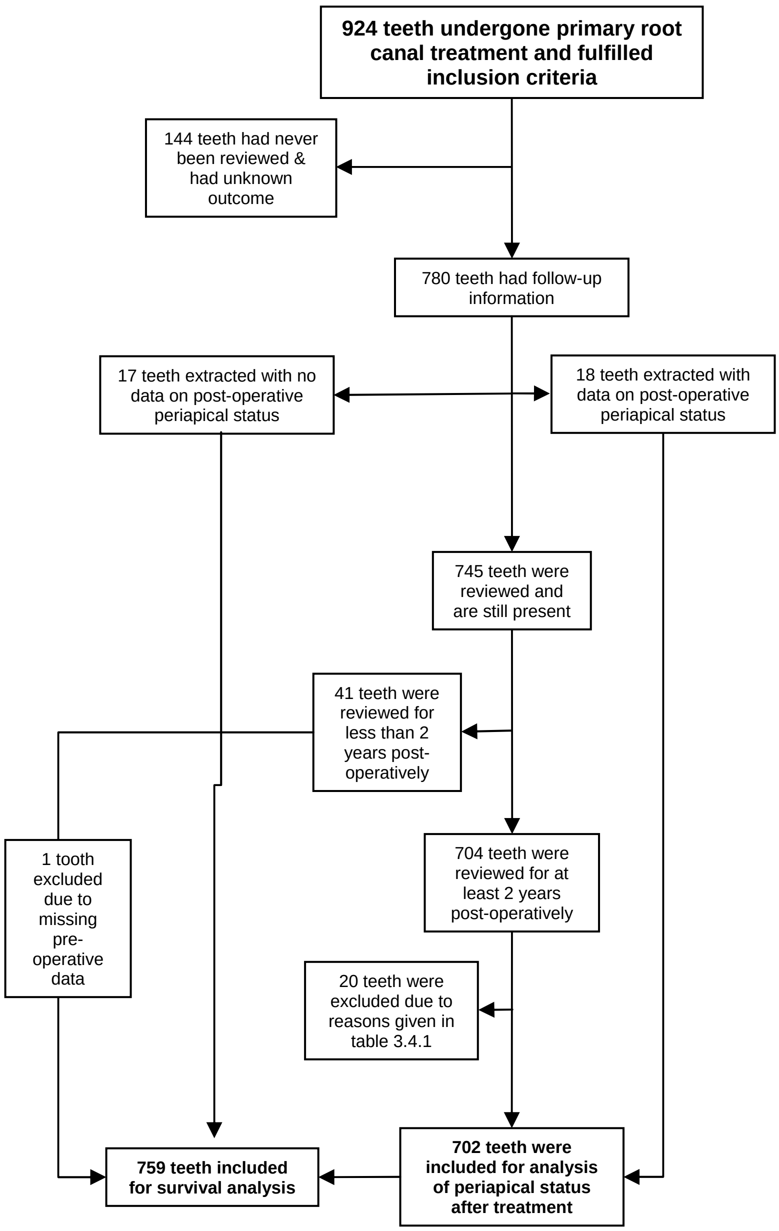
The pooled probabilities of tooth survival 2–10 years following root canal treatment ranged from 86% to 93%. There were substantial differences in study characteristics to hinder effective direct comparison of findings. The evidence on the prognostic factors for tooth survival was very weak. From the data available for meta-analyses, four conditions were identified to significantly improve tooth survival. They are listed in descending order of influence: (1) tooth restored with a crown after treatment; (2) teeth with mesial and distal proximal contacts; (3) tooth not functioning as abutment for removable or fixed prosthesis; and (4) non-molar teeth.

3.4 General results of prospective clinical study

3.4.1 Inclusion and exclusion of teeth following primary or secondary root canal treatment

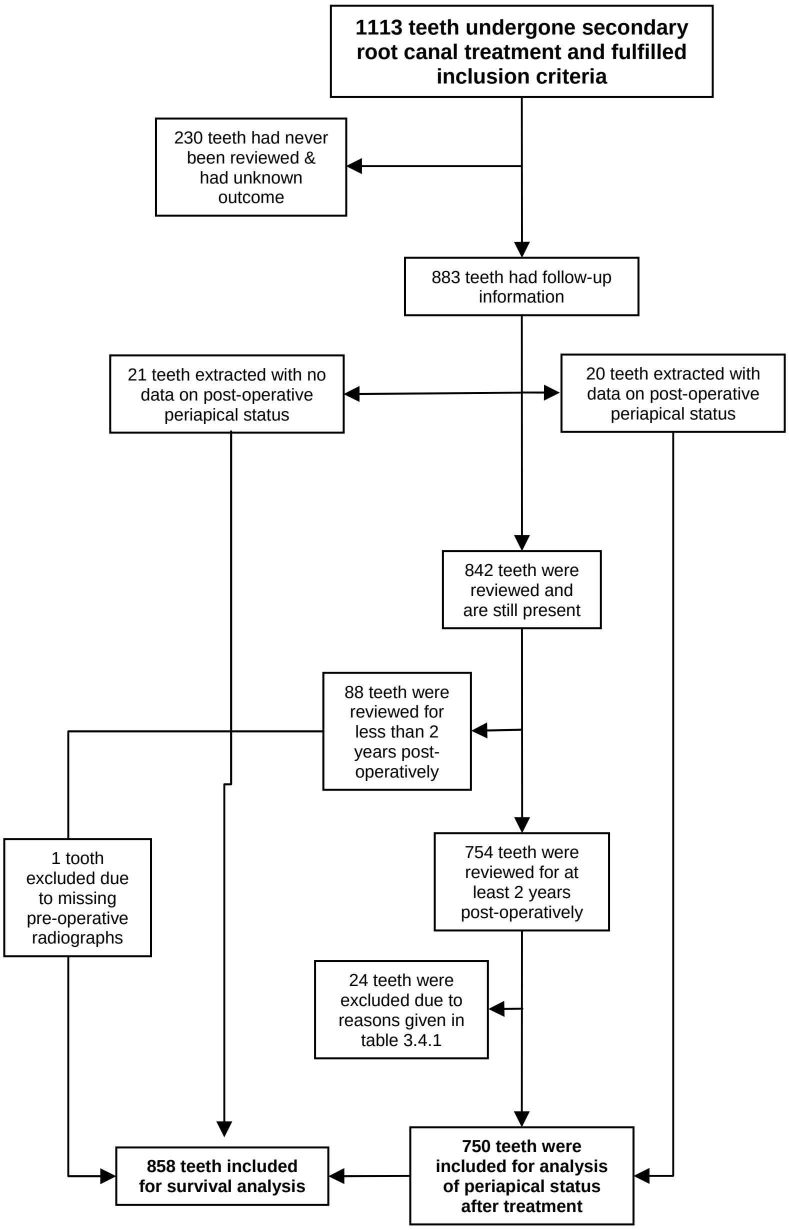
A total of 924 teeth had undergone primary root canal treatment and fulfilled inclusion criteria; of these 144 teeth had never been reviewed because the patients did not attend any of the review appointments (Figure 3.4.1).

Figure 3.4.1 Flow chart showing study-flow of teeth undergoing primary root canal treatment and fulfilling initial inclusion criteria



A total of 1113 teeth have undergone secondary root canal treatment and fulfilled inclusion criteria but 230 teeth were not reviewed as patients did not attend any of the review appointments (Figure 3.4.2).

Figure 3.4.2 Flow chart showing study-flow of teeth undergone secondary root canal treatment fulfilling initial inclusion criteria



The reasons for patients not attending the review appointment and the reasons for subsequent exclusion of teeth (20 and 24 teeth for primary and secondary root canal treatment, respectively) for analysis, using absence of periapical disease as outcome measure are presented in table 3.4.1.

Table 3.4.1 Reasons for patients' non-attendance at recall and for exclusion of teeth with at least 2 year follow-up

Reasons for not attending for recall	**Primary root canal treatment**	**Secondary root canal treatment**
No contact – unknown reason	117	189
Moved away	3	10
Deceased	3	3
Ill health / care home	1	1
Busy	20	27
Reasons for exclusion for those who had been followed up for 2 or more years		
Apex of roots not discernable on pre- or intra-operative radiographs	12	10
Pre- or intra-operative radiographs missing	4	6
Pre- or intra-operative data collection form missing	3	7
Tooth did not have final gutta-percha filling at the Eastman	1	0
Retreatment by referring dentist for unknown reason	0	1

The total number of patients, teeth and roots included in this prospective study are presented in Table 3.4.2. Of the teeth included, the number of teeth undergoing secondary root canal treatment was slightly larger than those undergoing primary root canal treatment.

Table 3.4.2 Number of cases included for the prospective analyses

	Patients	**Teeth**	**Roots**
Assessment of absence of clinical and radiographic signs of apical periodontitis after treatment			
1^{o}RCT	534	702	1170
2^{o}RCT	559	750	1314
Assessment of tooth survival after treatment			
1^{o}RCT	572	759	Not applicable
2^{o}RCT	642	858	Not applicable

1^{o}RCT = primary root canal treatment; 2^{o}RCT = secondary root canal treatment

The patients' age and gender distribution, as well as periapical status of excluded and included teeth for the analyses by absence of apical periodontitis after treatment are presented in table 3.4.3. The data revealed that the proportions of teeth with periapical lesion were larger amongst the studied teeth than amongst the excluded teeth, regardless of type of treatment (Table 3.4.3). The mean values of diameter of the periapical lesions of the studied teeth were also larger than that of the excluded teeth, regardless of type of treatment (Table 3.4.3).

Table 3.4.3 Characteristics of patients and teeth that were excluded from or included in the analyses of absence of clinical and radiographic signs of apical periodontitis after treatment

	Teeth not included		Teeth studied	
	1^oRCT (n = 222)	2^oRCT (n = 363)	1^oRCT (n = 702)	2^oRCT (n = 750)
Age (Mean)	38.2 yr	38.4 yr	41.5 yr	42.4 yr
Female	57.1%	58.3%	58.1 %	64.3 %
Male	42.9%	41.7%	41.9 %	35.7 %
Vital pulp	18.0%	–	19.2 %	–
Non-vital pulp	77.6%	–	80.8 %	–
Intact PDL	36.6%	28.4%	20.7 %	14.6 %
Widened PDL	4.4%	8.1%	13.0 %	11.2 %
Periapical lesion	53.7%	58.3%	66.3 %	74.2 %
Unable to assess peripaical status	5.4%	5.2%	–	–
Size of lesion (Mean)	1.7 mm	1.6 mm	2.9 mm	2.6 mm

1^oRCT = primary root canal treatment; 2^oRCT = secondary root canal treatment; PDL = periodontal ligament

3.4.2 Radiographic observer agreement

The author assessed all the radiographs and re-examined thirty percent of them at 1 year after the first assessment. The intra-observer agreement was good (Kappa 0.80; 95% CI: 0.77, 0.86).

A second observer who is an experienced Endodontist examined 30% of the radiographs and the inter-observer agreement was good (kappa 0.83; 95% CI 0.82, 0.89). In case of disagreement, the final decision was made by the author after discussion.

3.5 Results of investigation of primary or secondary root canal treatment outcome using absence of clinical and radiographic measures of apical periodontitis

3.5.1 Proportion of success by examination methods

By the end of the study period (2 – 4 years post-treatment), 91.3% (n = 1068) and 89.6% (n = 1178) of the roots from teeth which had undergone primary or secondary root canal treatment, respectively, were associated with no clinical signs or symptoms (Table 3.5.1a). There was an absence of periapical radiolucent lesion associated with 86.9% (n = 1017) and 84.6% (n = 1111) of the roots after primary and secondary root canal treatment, respectively. The distribution of different types of healing assessed by radiographic examination is presented in table 3.5.1b.

Table 3.5.1a–c Clinical signs & symptoms and radiographic outcome after root canal treatment

(a) Clinical examination	Total number of roots	Absence of signs and symptoms [number (%)]	Presence of signs and symptoms [number (%)]
1^{o}RCT	1170	1068 (91.3% [89.5%, 92.8%])	102 (8.7% [7.1%, 10.4%])
2^{o}RCT	1314	1178 (89.6% [87.9%, 91.2%])	136 (10.4% [8.8%, 12.1%])

(b) Radiographic examination	Total number of roots	Complete healing [Number (%)]	Incomplete healing [Number (%)]	Failed [Number (%)]
1^{o}RCT	1170	1017 (86.9% [84.9%, 88.8%])	85 (7.3% [5.8%, 8.9%])	68 (5.8% [4.5%, 7.3%])
2^{o}RCT	1314	1111 (84.6% [82.5%, 86.5%])	75 (5.7% [4.5%, 7.1%])	128 (9.7% [8.2%, 11.5%])

(c) Combined examinations	Total number of roots	Successful [Number (%)]	Unsuccessful [Number (%)]
1^{o}RCT	1170		
Strict criteria		969 (82.8% [80.5%, 84.9%])	201 (17.2% [15.0%, 19.3%])
Loose criteria		1043 (89.1% [87.4%, 90.9%])	127 (10.9% [9.1%, 12.6%])
2^{o}RCT	1314		
Strict criteria		1053 (80.1% [77.9%, 82.3%])	261 (19.9% [17.7%, 22.0%])
Loose criteria		1125 (85.6% [83.7%, 87.5%])	189 (14.4% [12.5%, 16.3%])

1^{o}RCT = primary root canal treatment; 2^{o}RCT = secondary root canal treatment

If treatment was only considered successful when both clinical and radiographic examinations revealed absence of apical periodontitis (namely strict criteria), primary and secondary root canal treatment were judged to be successful in 82.8% (n = 969) and 80.1% (n = 1053) of roots, respectively (Table 3.5.1c). The proportions of success based on loose criteria were 89.1% and 85.6% for primary and secondary root canal treatment, respectively (Table 3.5.1c).

The data on the number of years taken for a periapical lesion to heal (*based on radiographic examination alone*) were available for 277 of 639 completely healed lesions of primary root canal treatment cases and for 384 of 775 completely healed lesions of secondary root canal treatment cases (Table 3.5.2 – Overleaf). The majority of the 277 lesions associated with primary root canal treatment healed completely within one year (71.9%) and another large proportion healed completely between 1–2 years (19.4%) post-operatively. Similarly, the majority of the 384 lesions associated with secondary root canal treatment healed completely within 1 year (71.4%) and a similar large proportion between 1–2 years (24.2%) post-operatively. Only a small percentage (4.9% for primary root canal treatment; 4.5% for secondary root canal treatment) required 3 years or more to heal completely (Table 3.5.2). The factors affecting the rate of healing of periapical lesions were not investigated because of insufficient data.

Table 3.5.2 Number of years for complete resolution of periapical lesion

	1 year	2 year	3 year	4 year
1°RCT (n = 277)	207 (71.9%)	56 (19.4%)	14 (4.9%)	–
2°RCT (n = 384)	274 (71.4%)	93 (24.2%)	11 (2.9%)	6 (1.6%)

1°RCT = primary root canal treatment; 2°RCT = secondary root canal treatment

3.5.2 Identification of prognostic factors predicting success rate using logistic regression

Sections 3.5.2.1 to 3.5.2.5 present: (1) the proportion of roots with successful treatment by each potential prognostic factor; (2) the results of univariable logistic regression analyses investigating the effect of each potential prognostic factor on treatment outcome (allowing for clustering by patients); and (3) the effect of each significant factor adjusted for “pre-operative periapical status”. These analyses were performed separately for primary and secondary root canal treatment. *Section 3.5.2.6* summarises the factors which were found to have prognostic value from previous sections and subjected to further multiple regression analyses. *Section 3.5.2.7* presents the different stages of building of the final multiple logistic regression model using the combined primary and secondary root canal treatment dataset, and the goodness-of-fit statistics for checking of adequate fit of the final model.

3.5.2.1 Effects of patient characteristics and tooth/root morphological type

i) Patient factors

None of the patient factors (Table 3.5.3 – Overleaf) were found to have any significant effect on the success of either primary or secondary root canal treatment.

There was no effect of age (OR = 1) on the outcome of either type of treatment. Male patients were associated with lower odds of success than female patients regardless of type of treatment, although the observed differences were not significant and had very wide 95% confidence intervals (Table 3.5.3). This factor was therefore re-analysed after combining the primary and secondary root canal treatment datasets.

Table 3.5.3 Unadjusted effects of patient characteristics using logistic regression analysis

	Primary root canal treatment			Secondary root canal treatment		
Factors	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***
Age (continuous data)	–	–	1.004 (0.99, 1.01)	–	–	0.999 (0.99, 1.01)
Sex						
Female	699	84.4	1	864	81.4	1
Male	471	80.5	0.76 (0.56, 1.03)	450	77.8	0.80 (0.61, 1.06)
Diabetic						
No	1143	82.9	1	1283	80.1	1
Yes	27	77.8	0.72 (0.29, 1.80)	31	80.6	1.03 (0.42, 2.55)
Allergic						
No	881	82.3	1	1000	80.1	1
Yes	289	84.4	1.17 (0.81, 1.68)	314	80.3	1.01 (0.73, 1.39)
Systemic steroid						
No	1153	82.7	1	1294	80.3	1
Yes	17	88.2	1.56 (0.34, 6.70)	20	70.0	0.57 (0.22, 1.50)
Long term antibiotics						
No	1154	82.9	1	1307	80.1	1
Yes	16	75.0	0.62 (0.20, 1.93)	7	85.7	1.49 (0.18, 12.43)
Thyroxin therapy						
No	1120	82.8	1	1270	79.8	1
Yes	50	84.0	1.09 (0.51, 2.36)	44	90.9	2.54 (0.90, 7.16)
Hormone replacement						
No	1109	82.8	1	1279	80.4	1
Yes	61	83.6	1.06 (0.53, 2.12)	35	71.4	0.61 (0.29, 1.29)
Coronary heart disease						
No	1082	83.4	1	1217	79.8	1
Yes	88	76.1	0.63 (0.38, 1.07)	97	84.5	1.38 (0.78, 2.44)

'-' = number of roots and success rates stratified by each decade of age are presented in the Appendix X
*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients

The magnitude and/or direction of seven of the medical conditions on success were different for primary and secondary root canal treatment. The odds ratios for all the medical conditions had very wide 95% confidence intervals (Table 3.5.3). They were therefore not analysed further.

ii) Tooth and root morphology

Tooth type was found to have a significant effect on outcome of primary (Test for heterogeneity: $P = 0.01$) but not secondary (Test for heterogeneity: $P = 0.1$) root canal treatment. For both treatments, maxillary and mandibular molar teeth were associated with significantly higher odds of success than maxillary anterior teeth (Table 3.5.4 – Overleaf).

The success rates by root type were similar for both treatments except for the success rates of the mesio-buccal roots of maxillary molars and the mesial roots of mandibular molars (Table 3.5.4). The test for heterogeneity revealed that root type had a significant effect on outcome of both primary ($P = 0.05$) and secondary ($P < 0.0001$) root canal treatment.

The investigation of the effect of developmental anomalies of teeth was compromised by the number of teeth with such conditions.

Table 3.5.4 Unadjusted effects of tooth & root type and developmental anomaly using logistic regression analysis

Factors	Primary root canal treatment: No. of roots	Success rates (%)	Odds ratio (95% CI)*	Secondary root canal treatment: No. of roots	Success rates (%)	Odds ratio (95% CI)*
Tooth type			P = 0.01**			P = 0.1**
Upper incisors/canine	199	75.9	1	137	72.3	1
Upper premolars	81	72.8	0.85 (0.47, 1.53)	131	73.3	1.05 (0.61, 1.80)
Upper molars	413	87.2	2.16 (1.40, 3.33)	464	82.5	1.81 (1.16, 2.83)
Lower incisors/canine	74	73.0	0.86 (0.47, 1.57)	61	75.4	1.18 (0.59, 2.35)
Lower premolars	39	82.1	1.45 (0.60, 3.50)	48	83.3	1.92 (0.82, 4.47)
Lower molars	364	86.0	1.95 (1.28, 3.03)	473	82.2	1.78 (1.14, 2.77)
Root type			P = 0.05**			P < 0.0001**
Single rooted teeth	363	76.0	1	339	74.0	1
Buccal of 2 rooted premolar	26	69.2	0.71 (0.30, 1.69)	27	70.4	0.83 (0.35, 1.97)
Palatal of upper premolar/molar	161	85.7	1.89 (1.14, 3.13)	179	86.0	2.16 (1.33, 3.52)
Mesio-buccal of upper molar	131	85.5	1.86 (1.08, 3.20)	151	76.2	1.12 (0.92, 1.75)
Disto-buccal of upper molar	131	89.3	2.63 (1.44, 4.82)	148	87.2	2.39 (1.39, 4.08)
Mesial of lower molar	179	86.0	1.94 (1.19, 3.16)	233	77.7	1.22 (0.82, 1.81)
Distal of lower molar	177	85.9	1.92 (1.18, 3.12)	230	85.7	2.09 (1.34, 3.25)
Disto-lingual of lower molar	2	100.0	Not analysed	7	100.0	Not analysed
Developmental anomalies						
No	1160	83.0	1	1313	80.2	Not analysed
Yes	10	60.0	0.31 (0.09, 1.10)	1	0	

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factors

The effects of tooth and root types were investigated further by each being entered simultaneously with pre-operative periapical status into a regression model (Table 3.5.5). The test for heterogeneity for categorical factor only identified “root type” (P = 0.07 for primary treatment; P = 0.0007 for secondary treatment) but not “tooth type” (P = 0.2 for primary treatment; P = 0.4 for secondary treatment) to have prognostic value. Therefore only root type was investigated further in multiple regression models.

Table 3.5.5 Effects of tooth & root types adjusted for pre-operative periapical status using logistic regression analysis

Factors	Primary root canal treatment: Adjusted odds ratio (95% CI)*	Secondary root canal treatment: Adjusted odds ratio (95% CI)*
Tooth type	P = 0.2**	P = 0.4**
Upper incisors/canine	1	1
Upper premolars	0.91 (0.48, 1.76)	1.00 (0.57, 1.76)
Upper molars	1.53 (0.90, 2.60)	1.40 (0.84, 2.33)
Lower incisors/canine	0.78 (0.42, 1.43)	1.21 (0.60, 2.44)
Lower premolars	1.43 (0.55, 3.73)	1.95 (0.84, 4.53)
Lower molars	1.63 (0.97, 2.73)	1.45 (0.90, 2.35)
Root type	P = 0.07**	P = 0.0007**
Single rooted teeth	1	1
Buccal of 2 rooted premolar	1.14 (0.64, 2.05)	1.42 (0.71, 2.85)
Palatal of upper premolar/molar	1.65 (1.00, 2.72)	1.78 (1.09, 2.91)
Mesio-buccal of upper molar	1.24 (0.73, 2.09)	0.99 (0.64, 1.54)
Disto-buccal of upper molar	1.61 (0.95, 2.73)	1.94 (1.02, 2.67)
Mesial of lower molar	1.66 (1.02, 2.70)	1.09 (0.73, 1.63)
Distal of lower molar	1.62 (0.98, 2.65)	1.68 (1.07, 2.64)
Disto-lingual of lower molar	Not analysed	Not analysed

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factors

3.5.2.2 Effects of pre-operative factors

i) Pre-operative tooth factors common to both primary and secondary root canal treatment

Out of fourteen pre-operative factors, the *magnitude* and *direction* of the effects of seven factors (history of luxation injuries, soft tissue tenderness to palpation, swelling, sinus, periapical status, size of periapical lesion, root resorption) were similar for primary and secondary root canal treatment (Table 3.5.6 – Overleaf). The results indicated that presence of periapical lesion, larger lesions, and presence of the rest of the above conditions reduced the success of both treatments. The effect of "luxation injuries" on secondary root canal treatment was however not significant at the 5% level with very wide 95% confidence interval for the odds ratio.

When each of these seven factors was simultaneously entered with the factor "pre-operative periapical status" into a regression model, only two (presence of sinus, size of lesion) were found to have prognostic value for both primary and secondary root canal treatment (Table 3.5.7, page 167).

When analysing the effects of the size of lesion, "duration after treatment" was also entered into the model in addition to "pre-operative periapical status". However, the "duration after treatment" did not reach significance at the 5% level, regardless of whether it was primary or secondary root canal treatment.

"Swelling" was found to have prognostic value for secondary root canal treatment but not for primary root canal treatment after its effect was adjusted of pre-operative periapical status (Table 3.5.7).

Two other factors (periodontal probing depth [narrow base of endodontic origin], pulpal status) were significantly associated with the success rate of primary root canal treatment only (Table 3.5.6); pulpal status was not applicable to secondary root canal treatment by definition. When each factor was simultaneously entered with periapical status into a regression model (Table 3.5.7) both factors retained significance at the 5% level. Teeth with non-vital pulp or periodontal probing defect extending deeper than 5 mm were associated with lower odds of success. These two factors were therefore further analysed in multiple regression models.

"Root perforation" was, on the other hand, significantly associated with the success rate of secondary root canal treatment but not with the success rate of primary root canal treatment (Table 3.5.6). This factor was subsequently converted into a binary variable (Table 3.5.7) for analysis with pre-operative status in a statistical model and found to retain significance at the 5% level.

Table 3.5.6 Unadjusted effects of pre-operative tooth factors (common to both primary and secondary root canal treatment) using logistic regression analysis

	Primary root canal treatment			Secondary root canal treatment		
Factors	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***
History of luxation injuries						
No	1012	83.9	1	1249	80.5	1
Yes	158	75.9	0.61 (0.41, 0.91)	65	72.3	0.63 (0.36, 1.11)
History of tooth fracture or crack			P = 0.4**			P = 0.7**
No	949	83.0	1	1119	80.6	1
Fracture	121	86.0	1.25 (0.93, 2.14)	96	78.1	0.86 (0.52, 1.43)
Cracks	100	77.0	0.68 (0.42, 1.12)	99	76.8	0.79 (0.49, 1.30)
Restoration type			P = 0.3**			P = 0.2**
Virgin tooth	179	77.1	1	–	–	–
Plastic restoration	454	83.7	1.53 (0.99, 2.34)	663	81.7	2.24 (0.89, 5.67)
Plastic + post	–	–	–	10	70.0	1.16 (0.23, 5.95)
Cast restoration	280	81.4	1.30 (0.82, 2.07)	454	81.1	2.14 (0.84, 5.46)
Cast restoration + post	10	80.0	1.19 (0.24, 5.82)	63	71.4	1.25 (0.43, 3.61)
Temporary dressing	225	87.6	2.09 (1.23, 3.54)	103	74.8	1.48 (0.54, 4.07)
Open cavity	22	81.8	1.34 (0.43, 4.17)	21	66.7	1
Pain						
No	682	84.0	1	722	80.2	1
Yes	488	81.1	0.82 (0.60, 1.11)	592	80.1	0.99 (0.76, 1.30)
Tenderness to percussion						
No	697	81.3	1	686	80.8	1
Yes	473	85.0	1.30 (0.94, 1.78)	628	79.5	0.92 (0.70, 1.21)
Soft tissue tenderness						
No	840	84.5	1	866	82.6	1
Yes	330	78.5	0.67 (0.48, 0.92)	448	75.4	0.65 (0.49, 0.86)
Soft tissue swelling						
No	1047	83.7	1	1187	81.3	1
Yes	123	75.6	0.61 (0.39, 0.94)	127	69.3	0.52 (0.35, 0.78)
Sinus						
No	1029	85.0	1	1178	82.4	1
Yes	141	66.7	0.35 (0.24, 0.52)	136	60.3	0.32 (0.22, 0.47)
Periodontal probing depth			P = 0.001**			
<5mm	1128	83.7	1	1276	80.2	1
≥5mm but not to apex	36	66.7	0.39 (0.19, 0.79)	38	78.9	0.93 (0.42, 2.05)
Extended to apex	6	16.7	0.04 (0.01, 0.34)	–	–	–
Pulpal status						
non-vital	912	80.6	1	–	–	–
Vital	258	90.7	2.35 (1.50, 3.69)	–	–	–
Periapical status			P < 0.0001**			P < 0.0001**
Intact PDL	387	92.5	1	376	89.1	1
Widened PDL	169	87.0	0.54 (0.30, 0.97)	175	89.7	1.07 (0.59, 1.92)
Periapical lesion	614	75.6	0.25 (0.16, 0.38)	763	73.5	0.34 (0.24, 0.49)
Size of periapical lesion						
Continuous (*each mm*)	–	–	0.83 (0.80, 0.88)	–	–	0.75 (0.71, 0.80)
<5mm	992	85.7	1	1179	83.2	1
≥5mm	178	66.9	0.34 (0.24, 0.48)	135	53.3	0.23 (0.16, 0.33)
Root resorption			P = 0.09**			P = 0.04**
No	1072	83.6	1	1238	80.9	1
Internal	20	90.0	1.77 (0.41, 7.68)	9	88.9	1.89 (0.24, 15.22)
External (apical)	57	70.2	0.46 (0.26, 0.83)	64	65.6	0.45 (0.26, 0.77)
External (lateral)	10	80.0	0.79 (0.17, 3.73)	3	66.7	0.47 (0.04, 5.24)
Internal & external apical	2	100.0	Not analysed	0	0	–
Cervical	9	55.6	0.25 (0.07, 0.92)	0	0	–
Root perforation						P = 0.02**
None	1156	82.7	1	1288	80.4	1
Apical	–	–	–	2	100.0	Not analysed
Sub-crestal	2	100.0	Not analysed	10	40.0	0.16 (0.05, 0.58)
Supra-osseous	12	91.7	2.30 (0.29, 17.53)	14	78.6	0.89 (0.25, 3.22)

PDL = Periodontal ligament space
*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factors

Table 3.5.7 Effects of potential common significant pre-operative tooth factors adjusted for pre-operative periapical status using logistic regression analysis

	Primary root canal treatment	**Secondary root canal treatment**
Factors	**Odds ratio (95% CI)***	**Odds ratio (95% CI)***
Luxation injuries		
No	1	1
Yes	0.83 (0.54, 1.28)	0.79 (0.45, 1.40)
Soft tissue tenderness		
No	1	1
Yes	0.78 (0.53, 1.15)	0.74 (0.52, 1.04)
Swelling		
No	1	1
Yes	0.71 (0.42, 1.20)	0.55 (0.34, 0.90)
Sinus		
No	1	1
Yes	0.50 (0.32, 0.78)	0.38 (0.23, 0.62)
Pulpal status		
Non-vital	1	–
Vital	1.78 (1.10, 2.87)	–
Periodontal probing depth (*narrow in width*)	P = 0.0009**	
<5mm	1	1
≥5mm but not extended to apex	0.50 (0.24, 1.05)	0.95 (0.39, 2.36)
Extended to apex	0.06 (0.01, 0.43)	–
Size of periapical lesion (Continuous)	0.89 (0.84, 0.95)	0.84 (0.78, 0.90)
Duration of after treatment (months)	1.01 (1.00, 1.02)	1.00 (0.98, 1.01)
Root resorption	P = 0.2**	P = 0.3**
No	1	1
Internal	1.12 (0.57, 2.17)	1.20 (0.57, 2.56)
External (apical)	0.72 (0.40, 1.28)	0.59 (0.32, 1.09)
External (lateral)	1.08 (0.23, 5.07)	0.52 (0.05, 5.21)
Internal & external apical	Not analysed	–
Cervical	0.42 (0.13, 1.37)	–
Root perforation		
None / apical	Not analysed	1
Subcrestal / supra-osseous		0.32 (0.13, 0.79)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor

ii) <u>Pre-operative tooth factors unique to secondary root canal treatment</u>

Out of five factors, four (satisfactory root filling, type of foreign material, type of fractured instrument, fate of foreign material) were found to have significant ($P < 0.05$) effects on the success rate of secondary root canal treatment (Table 3.5.8 – Overleaf). When each of the 4 factors was entered simultaneously with pre-operative periapical status, “type of foreign material”, “type of fractured instrument” and “fate of foreign material” were found to have prognostic value (Table 3.5.8). These three factors were further analysed in multiple regression models.

Foreign material present in 1241 roots undergoing secondary root canal treatment was removed completely in the majority (92%, n=1146) and remained the same (4.5%, n=56) or some remained in the canal albeit bypassed during instrumentation in a small proportion of cases (2%, n=25) (Table 3.5.8). The material was extruded into the periapical tissues during removal in 1% (n=14) of the roots (Table 3.5.8). Successful removal or bypassing of the foreign material was associated with significantly higher success rates (Table 3.5.8).

Fractured instruments were present in 94 roots and just over half of these were removed (28.7%) or bypassed during canal preparation (23.4%) (Table 3.5.9). H-files (43%) were removed more often than K-files (18%). However, there was a higher risk of extruding an H-file (14%).

Table 3.5.8 Unadjusted and adjusted effects of pre-operative tooth factors, unique to secondary root canal treatment, using logistic regression analysis

Factors	No. of roots	Success rates (%)	Unadjusted odds ratio (95% CI)*	§Adjusted odd ratio (95% CI)*
Satisfactory root filling				
No	1048	81.3	1	1
Yes	266	75.6	0.71 (0.52, 0.98)	0.89 (0.63, 1.24)
Canal content			P = 0.6**	
Un-instrumented	59	84.7	1	
Empty but instrumented	14	71.4	0.45 (0.12, 1.75)	Not analysed
Foreign material	1241	80.0	0.72 (0.35, 1.49)	
Type of foreign material			P = 0.007**	P < 0.0001**
$Ca(OH)_2$	8	37.5	0.14 (0.03, 0.60)	0.18 (0.03, 0.93)
Gutta-percha	1026	80.9	1	1
Cement	39	84.6	1.30 (0.54, 3.14)	0.88 (0.37, 2.05)
Thermafil®	10	60.0	0.35 (0.10, 1.27)	0.52 (0.09, 3.10)
Silver point	64	87.5	1.65 (0.78, 3.52)	1.13 (0.63, 2.03)
Fractured instrument	94	69.1	0.53 (0.33, 0.84)	0.54 (0.34, 0.86)
Type of fractured instrument			P = 0.02**	P = 0.01**
None	1220	81.0	1	1
K-file	49	67.3	0.48 (0.26, 0.89)	0.61 (0.32, 1.18)
H-file	28	71.4	0.59 (0.26, 1.35)	0.62 (0.28, 1.33)
NiTi	3	100.0	Not analysed	Not analysed
Spiral filler	11	54.5	0.28 (0.09, 0.93)	0.40 (0.08, 1.91)
Gates Glidden drill	3	100.0	Not analysed	Not analysed
Fate of foreign material			P < 0.0001**	P < 0.0001**
Remained the same	56	51.8	1	1
Bypassed	25	84.0	4.89 (1.49, 16.08)	3.74 (1.34, 10.46)
Removed	1146	81.8	4.17 (2.42, 7.20)	3.50 (1.94, 6.31)
Extruded apically	14	42.9	0.70 (0.21, 2.28)	1.01 (0.32, 3.26)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factors §Odds ratio adjusted for pre-operative periapical status

Table 3.5.9 Fate of fractured instruments by type of instrument

Type of fractured instrument	Total	Remained as pre-operatively	Bypassed	Removed	Extruded apically
K-file	49	25 (51.0%)	15 (30.6%)	9 (18.4%)	0
H-file	28	9 (32.1%)	3 (10.7%)	12 (42.9%)	4 (14.3%)
NiTi instrument	3	0	2 (66.7%)	1 (33.3%)	0
Spiral filler	11	5 (45.5%)	1 (9.1%)	5 (45.5%)	0
Gates Glidden drill	3	1 (33.3%)	1 (33.3%)	0	1 (33.3%)
Total	**94 (100%)**	**40 (42.6%)**	**22 (23.4%)**	**27 (28.7%)**	**5 (5.3%)**

3.5.2.3 Effects of operator's qualification, prediction of prognosis and treatment visits

Most of the root canal treatments were performed by 1st year postgraduate students, less frequently by 2nd year students and least by staff members, regardless of primary or secondary type (Table 3.5.10 – Overleaf). For primary root canal treatment cases, the success rates of treatment by operator experience were similar (Table 3.5.10). On the other hand, the success rates of secondary root canal treatment increased with the experience of the operator, although the difference was not statistically significant. This trend remained the same when this factor was analysed with adjustment to pre-operative periapical status in a regression model, although it did not reach the 5% significance level (*results not shown*). This factor was therefore not analysed further.

Table 3.5.10 Unadjusted effects of operator's qualification & prediction of prognosis and treatment visits using logistic regression analysis

	Primary root canal treatment				Secondary root canal treatment		
Factors	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***		**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***
Operator's experience			P = 0.7**				P = 0.4**
1st year students	747	83.1	1		796	78.8	1
2nd year students	314	81.2	0.88 (0.62, 1.23)		407	81.3	1.17 (0.87, 1.59)
Staff member	109	85.3	1.18 (0.67, 2.07)		111	85.6	1.60 (0.92, 2.79)
Estimated endodontic prognosis by operator							
Poor	24	66.7	Not analysed		28	71.4	Not analysed
Fair	173	85.5			363	83.7	
Good	421	86.5			310	83.2	
Number of treatment visits							
1	14	100.0	Not analysed		3	66.7	Not analysed
2	434	83.2			425	81.6	
3	427	82.7			453	81.5	
4	167	85.0			289	78.2	
5	92	82.6			85	67.1	
6	22	68.2			39	92.3	
7	11	72.7			8	75.0	
8	0	–			12	83.3	
9	3	0.0			–	–	

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor

Operators' compliance in recording their estimated prognosis of root canal treatment was poor. Although it was a routine clinical practice to inform the patient about the prognosis of the treatment during options analysis, information on the estimated prognosis were however only available for 53% of the roots undergoing primary (n=618) and secondary (n = 701) root canal treatment. Despite the apparent reluctance to record the prognosis, when designated "poor" the success rate *was* lower; whilst there was no real difference in success between those designated "fair" or "good" (Table 3.5.10). Due to the large proportion (48%) of missing data and the small proportion estimated as "poor prognosis", the association of this factor with success of treatment was not analysed further.

Most of the treatments were carried out over multiple visits regardless of whether it was primary or secondary root canal treatment (Table 3.5.10). For primary root canal treatment (Table 3.5.10), all treatments performed over 1 visit were successful. The success rates for primary root canal treatment carried out over 2–5 visits (83%–85%) were reduced by over 10% and the success rates were reduced further for those requiring 6–7 visits to complete (68%–73%). For secondary root canal treatment (Table 3.5.10), the lowest success rate (66.7%) was registered in three single-rooted teeth completed in one visit. Amongst those roots undergoing multiple-visit treatment, there was no obvious trend in the success rate by the number of treatment visits. Due to the potential influence of unrecorded confounders underlying number of treatment visits, such as the operator skill, biological or technical case complexity, patient compliance, this factor was not analysed further.

3.5.2.4 Effects of intra-operative factors

i) Preparation of teeth prior to root canal treatment

Prior to commencement of treatment, an orthodontic or a copper band was placed on a proportion of teeth in order to protect them from fracturing or to aid retention of the temporary restoration for coronal seal during treatment. They were placed in a similar proportion of teeth amongst primary (28.2%, 331 roots) and secondary (24.8%, 326 roots) root canal treatment cases (Table 3.5.11).

Their placement was associated with higher success rates for both types of treatment; reaching a 5% significant level for primary root canal treatment but not for secondary root canal treatment (Table 3.5.11). When this factor was entered simultaneously with pre-operative periapical status in a model, it was found to have no prognostic value (Table 3.5.11), regardless of type of treatment.

Table 3.5.11 Unadjusted and adjusted effects of protection of tooth with metal band using logistic regression analysis

	Primary root canal treatment				Secondary root canal treatment		
Factors	No. of roots	Success rates (%)	Odds ratio (95% CI)*		No. of roots	Success rates (%)	Odds ratio (95% CI)*
Protect the tooth with a band							
No	839	80.9	1		988	79.3	1
Yes	331	87.6	[u]1.67 (1.15, 2.41) [a]1.48 (0.93, 2.37)		326	82.8	[u]1.26 (0.91, 1.75) [a]1.19 (0.79, 1.81)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
[U]Unadjusted odds ratio; [a]Odds ratio adjusted for pre-operative periapical status

ii) Location of canals

Magnification with optical loupes or microscope was used less often during primary (21.6%, 253 roots) than secondary (43.2%, 567 roots) root canal treatment to aid location of canal orifice, removal of foreign materials or repair of perforations. Their use was not however, significantly associated with the improved success of primary or secondary root canal treatment (Table 3.5.12 – Overleaf). Thus this factor was not analysed further.

The prevalence of roots with a second canal located and treated was lower among primary (25.0%, 292 roots) than secondary (31.4%, 412 roots) root canal treatment cases (Table 3.5.12). This factor had no significant influence on the success of primary or secondary root canal treatment (Table 3.5.12); therefore it was not analysed further.

Table 3.5.12 Unadjusted effects of intra-operative factors (location of canals) using logistic regression analysis

Factors	Primary root canal treatment: No. of roots	Success rates (%)	Odds ratio (95% CI)*	Secondary root canal treatment: No. of roots	Success rates (%)	Odds ratio (95% CI)*
Use of magnification						
No	917	82.1	1	747	79.8	1
Yes	253	85.4	1.27 (0.86, 1.87)	567	80.6	1.05 (0.80, 1.38)
Second canal found						
No	878	82.3	1	902	81.5	1
Yes	292	84.2	1.15 (0.80, 1.64)	412	77.2	0.77 (0.58, 1.02)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients

When the data for all types of roots were pooled, the majority (82%) of the additional canals in roots undergoing primary root canal treatment were located without the aid of magnification. In contrast, magnification was employed for locating 43% of additional canals in roots undergoing secondary root canal treatment (Table 3.5.13).

Table 3.5.13 Number and percentage of roots with additional canal located by the use of magnification

	Primary root canal treatment		Secondary root canal treatment	
	Any root type (n = 292)	Mesio-buccal root of maxillary molars (n = 33)	Any root type (n = 412)	Mesio-buccal root of maxillary molars (n = 50)
Use of magnification	49 (16.8%)	6 (18.2%)	178 (43.2%)	32 (64.0%)
Without magnification	243 (82.2%)	27 (81.8%)	234 (56.8%)	18 (36.0%)

Amongst the mesio-buccal roots of maxillary molar teeth, the majority (82%) of additional canals were located without the use of magnification during primary root canal treatment (Table 3.5.13). In contrast, the majority (64%) of second mesio-buccal canals amongst the secondary root canal treatment cases were located with the use of magnification (Table 3.5.13). The treatment of one or more canals in the mesio-buccal root of maxillary molars made no obvious difference to the success rate, regardless of treatment type (primary or secondary) (Table 3.5.14).

Table 3.5.14 Success rates by number of canals treated, type of treatment and periapical status of mesio-buccal roots in maxillary molar teeth

	Primary root canal treatment			Secondary root canal treatment		
	Intact PDL	**Widened PDL**	**Periapical lesion**	**Intact PDL**	**Widened PDL**	**Periapical lesion**
1 canal	91.5% (43/47)	92.3% (12/13)	73.7% (28/38)	88.9% (24/27)	100.0% (12/12)	69.4% (43/62)
>=2 canals	100.0% (10/10)	100.0% (7/7)	75.0% (12/16)	81.8% (9/11)	83.3% (5/6)	66.7% (22/33)

PDL = periodontal ligament space

iii) Mechanical enlargement and shaping of canals

The majority of the canals were enlarged and shaped using stainless steel files, regardless of whether it was primary (86%, 1004 roots) or secondary (87%, 1144 roots) root canal treatment (Table 3.5.15). The use of NiTi rotary instrument was found to be significantly associated with higher success rate of secondary root canal treatment (Table 3.5.15). However, the test for heterogeneity revealed this categorical factor to have no prognostic value for either treatment (Table 3.5.15).

Table 3.5.15 Unadjusted effects of intra-operative factors (canal negotiation and enlargement) using logistic regression analysis

	Primary root canal treatment			Secondary root canal treatment		
Factors	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***
Instrument type			P = 0.4**			P = 0.1**
Stainless steel file	1004	82.0	1	1144	78.9	1
Hand NiTi	52	88.5	1.68 (0.71, 4.01)	47	89.4	2.24 (0.88, 5.73)
Rotary NiTi	114	87.7	1.57 (0.88, 2.81)	123	87.8	1.92 (1.10, 3.36)
Patent at apical terminus						
No	76	76.3	1	184	69.6	1
yes	1094	83.3	1.54 (0.89, 2.68)	1130	81.9	1.97 (1.39, 2.80)
Apical extent of instrumentation						
Each mm short of EAL ‘0’ position (*continuous variable*)	–	–	0.91 (0.82, 1.02)	–	–	0.82 (0.76, 0.91)
Binary variable:						
≤2mm	1141	83.2	2.23 (1.00, 4.96)	1216	81.5	2.56 (1.65, 3.95)
>2mm	29	69.0	1	98	63.3	1
≤1mm	1099	83.1	1.32 (0.70, 2.44)	1154	81.5	1.89 (1.25, 2.86)
>1mm	71	78.9	1	160	70.0	1
Initial apical size of canal						
(continuous: 0 – 300)	–	–	0.987 (0.980, 0.995)	–	–	1.00 (0.99, 1.01)
≤30	1069	84.0	1	1144	80.8	1
>30	101	70.3	0.45 (0.29, 0.71)	170	75.9	0.75 (0.51, 1.10)
Apical size of preparation						
(continuous: 20 – 300)	–	–	0.98 (0.98, 0.99)	–	–	1.00 (0.99, 1.01)
≤30	812	85.7	1	791	81.4	1
>30	358	76.3	0.54 (0.39, 0.73)	523	78.2	0.82 (0.62, 1.08)
Taper of preparation			P = 0.006**			P = 0.2**
.02	8	37.5	0.12 (0.03, 0.51)	31	71.0	0.70 (0.31, 1.55)
.04	14	71.4	0.50 (0.15, 1.62)	0	–	–
.05	524	83.4	1	537	77.8	1
.06	125	86.4	1.26 (0.72, 2.22)	132	89.4	2.40 (1.33, 4.33)
.08	18	94.4	3.38 (0.44, 25.77)	23	78.3	1.02 (0.37, 2.82)
.10	481	81.9	0.90 (0.65, 1.25)	591	80.7	1.19 (0.89, 1.59)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factors

Although roots with “patency at apical terminus” were shown to have a higher success rate for both treatments (Table 3.5.15), its effect was only significant at the 5% level for secondary root canal treatment cases. Its prognostic value remained after its effect was adjusted for pre-operative periapical status (Table 3.5.16 – Overleaf). This factor was therefore analysed further using multiple logistic regression.

The magnitude and direction of the effect of “apical extent of instrumentation” was similar for both treatments (Table 3.5.15, page 172). This factor remained significant at the 5% level when the result of the analysis was adjusted for pre-operative periapical status (Table 3.5.16). This factor was therefore analysed further using multiple logistic regression.

Table 3.5.16 Effects of potential significant intra-operative factors adjusted for pre-operative periapical status using logistic regression analysis

	Primary root canal treatment	**Secondary root canal treatment**
Factors	**Odds ratio (95% CI)***	**Odds ratio (95% CI)***
Patent at apical foramen		
No	1	1
yes	1.68 (0.81, 3.45)	2.37 (1.64, 3.44)
Apical extent of instrumentation (mm from AL “0” reading) (continuous)	0.85 (0.76, 0.95)	0.84 (0.76, 0.91)
Initial apical size of canal		
(continuous: 0 – 300)	0.99 (0.99, 1.00)	1.00 (1.00, 1.01)
≤30	1	1
>30	0.66 (0.45, 0.98)	1.09 (0.76, 1.56)
Apical size of preparation		
(continuous: 0 – 300)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)
≤30	1	1
>30	0.72 (0.58, 0.91)	1.07 (0.86, 1.34)
Taper of preparation	P = 0.05**	Not analysed
.02	0.19 (0.06, 0.64)	
.04	0.49 (0.17, 0.14)	
.05	1	
.06	1.18 (0.53, 2.61)	
.08	3.46 (0.41, 28.84)	
.10	1.02 (0.67, 1.56)	

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor

When the “initial apical size of canal” and “apical size of the canal preparation” were analysed as a continuous variable, they were significantly associated negatively with the success of primary (Table 3.5.15 – Overleaf) but had no effect on secondary root canal treatment. When the two factors were dichotomised at ISO size 30, the success rate for both treatments were lower in those roots with initial or prepared canal sizes larger than ISO 30 (Table 3.5.15). Again, this observation was only significant for primary root canal treatment cases. Their effects remained statistically significant at the 5% level when the results of the analyses were adjusted for the pre-operative periapical status (Table 3.5.15). Clinically, the “apical size of canal preparation” was bound to be dictated by the “initial apical size of canal” in those roots with initially large canals. Therefore, only the “apical size of canal preparation” was investigated further in multiple regression models.

The taper of canal preparation was initially found to have a significant effect on the success of primary (P = 0.006) but not secondary (P = 0.2) root canal treatment (Table 3.5.15). Canals with narrow taper (< .05) had the lowest success rates regardless of whether it was primary or secondary root canal treatment, followed by canals with .05 or .10 tapers and then canals with .06 or .08 tapers. Its prognostic value for primary root canal treatment was retained even after adjusting for the pre-operative periapical status (Table 3.5.16, page 173). This factor was therefore investigated further using multiple logistic regression models.

v) Procedural errors and management

Procedural errors including canal perforation (3%, 0.9%), canal blockage (6%, 1%) and instrument fracture (1%, 0.9%) were more prevalent amongst primary than secondary root canal treatment cases, respectively (Table 3.5.17).

The occurrence of these errors was however, associated with significantly ($p < 0.05$) lower success rate of secondary root canal treatment but their effects on that of primary root canal treatment were of much smaller magnitude and were not significant at the 5% level (Table 3.5.17). After adjusting their effects on the success of secondary root canal treatment for pre-operative status, one factor, "fracture of instrument", failed to retain its prognostic value (Table 3.5.17). The factors "perforation" and "blockage of canal" were therefore analysed further in multiple logistic regression models.

For cases with pre- or intra-operative perforation, glass ionomer cement was the most commonly used material for repair of perforations at the coronal level. There was no obvious difference in the success rate by different repair materials used (Table 3.5.17). The effect of this factor was not investigated further due to the small number of cases.

Table 3.5.17 Unadjusted and adjusted effects of intra-operative factors (procedural error and perforation repair material) using logistic regression analysis

	Primary root canal treatment			Secondary root canal treatment		
Factors	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***
Perforation						
No	1134	82.8	1	1302	80.4	1
Yes	36	83.3	[U]1.04 (0.43, 2.53) [a]0.89 (0.18, 1.62)	12	50.0	[U]0.24 (0.02, 0.76) [a]0.26 (0.07, 0.94)
Blockage of canal						
No	1100	83.2	1	1298	80.4	1
Yes	70	77.1	[U]0.68 (0.38, 1.22) [a]0.68 (0.32, 1.45)	16	56.3	[U]0.31 (0.12, 0.85) [a]0.35 (0.12, 0.99)
Fracture of instrument						
No	1155	82.9	1	1302	80.4	1
Yes	15	80.0	[U]0.83 (0.23, 2.96) [a]0.83 (0.47, 1.48)	12	50.0	[U]0.24 (0.08, 0.76) [a]0.41 (0.13, 1.27)
Perforation repair material						
EBA/IRM®	2	100.0	Not analysed	4	50.0	Not analysed
Glass ionomer cement	23	82.6		19	63.2	
MTA™	7	85.7		7	57.1	
Gutta-percha	10	90.0		7	71.4	
Amalgam	1	100.0		1	0.0	

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
[U]Unadjusted odds ratio; [a]Odds ratio adjusted for pre-operative periapical status

vi) Chemical debridement of root canal

All the teeth/roots were irrigated with sodium hypochlorite solution (NaOCl) with a concentration of 2.5% being used in the majority of roots (92%), regardless of whether the case was primary (1082/1170) or secondary (1214/1314) root canal treatment (Table 3.5.18). The concentration of NaOCl was found to have no significant effect on the success rate of either treatment (Table 3.5.18).

Table 3.5.18 Unadjusted and adjusted effects of intra-operative factors (chemical debridement of root canal) using logistic regression analysis

Factors	Primary root canal treatment: No. of roots	Primary: Success rates (%)	Primary: Odds ratio (95% CI)*	Secondary root canal treatment: No. of roots	Secondary: Success rates (%)	Secondary: Odds ratio (95% CI)*
NaOCl concentration						
2.5%	1082	82.8	1	1214	80.3	1
4–5%	88	83.0	[U]1.01 (0.57, 1.80)	100	78.0	[U]0.87 (0.53, 1.42)
Irrigation solution						
NaOCl alone	834	83.1	1	747	79.3	1
NaOCl + other**	336	82.1	[U]0.94 (0.67, 1.31)	567	81.3	[U]1.14 (0.86, 1.50)
Additional use of iodine						
No	1088	83.2	1	1018	80.5	1
Yes	82	78.0	[U]0.72 (0.42, 1.24) [a]0.92 (0.49, 1.76)	296	79.1	[U]0.92 (0.67, 0.13) [a]0.92 (0.63, 1.34)
Additional use of CHX						
No	1129	83.4	1	1172	80.8	1
Yes	41	65.9	[U]0.38 (0.20, 0.74) [a]0.40 (0.18, 0.88)	142	74.6	[U]0.70 (0.47, 1.05) [a]0.78 (0.45, 1.33)
Additional use of EDTA						
No	887	82.3	1	942	77.5	1
Yes	283	84.5	[U]1.17 (0.81, 1.68) [a]1.06 (0.69, 1.63)	372	86.8	[U]1.91 (1.37, 2.68) [a]1.93 (1.27, 2.93)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
[U]Unadjusted odds ratio; [a]Odds ratio adjusted for pre-operative periapical status
**Other irrigation solutions included 10% povidone iodine, 0.2% chlorhexidine gluconate (CHX), 17% ethylene-diamine-tetra-acetic acid (EDTA)

In 28.7% (336/1170) and 43.2% (567/1314) of the roots, one or more other types of irrigant were also used during primary or secondary root canal treatment, respectively (Table 3.5.18). They included: Betadine®, Corsodyl® and EDTA. The additional use of other irrigants had no significant effect on the success rate of either treatment (Table 3.5.18). When the analyses were stratified by the different types of additional irrigant, they were found to have different effects on the success of primary and secondary root canal treatment (Table 3.5.18). The additional use of Betadine® had no beneficial or detrimental effect on the success of either type of treatment. Whereas, the additional use of Corsodyl® was associated with a lower success rate for both treatments although statistical significance at the 5% level was only reached for primary root canal treatment cases. In contrast, the additional use of EDTA did not have any effect on the success of primary root canal treatment but was associated with a significantly higher success rate for secondary root canal treatment (Table 3.5.18). The effects of Corsodyl® and EDTA remained significant at the 5% level after the results were adjusted for pre-operative periapical status (Table 3.5.18). These two factors were investigated further in multiple regression models as well as in the combined analyses for their potential interaction with the type of treatments.

The effect of inter-appointment medicament could not be analysed in this study because $Ca(OH)_2$ paste was used in 98% of primary or secondary root canal treatment cases.

vii) Inter-appointment complications

Only those cases completed over multiple visits (n=1156 for primary root canal treatment; n=1311 for secondary root canal treatment) were included in the analysis of the effects of inter-appointment complications on success rates. The prevalence of inter-appointment pain (11.9% [138/1156] for primary treatment, 18.2% [238/1311] for secondary treatment) was higher than that of inter-appointment swelling (2.9% [34/1156] for primary treatment, 3.0% [39/1311] for secondary treatment), regardless of the type of treatment (Table 3.5.19).

Table 3.5.19 Unadjusted and adjusted effects of intra-operative factors (inter-appointment complications) using logistic regression analysis

	Primary root canal treatment			Secondary root canal treatment		
Factors	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***
Inter-appointment pain						
No	1018	83.7	1	1073	80.7	1
Yes	138	75.4	[U]0.60 (0.39, 0.91) [a]0.55 (0.32, 0.95)	238	77.7	[U]0.84 (0.59, 1.18) [a]0.83 (0.53, 1.29)
Inter-appointment swelling						
No	1122	83.3	1	1272	80.4	1
Yes	34	61.8	[U]0.33 (0.16, 0.66) [a]0.30 (0.12, 0.76)	39	71.8	[U]0.62 (0.30, 1.26) [a]0.70 (0.31, 1.61)
Use of systemic antibiotics						
No	1131	83.0	1	1302	80.1	1
Yes	25	68.0	[U]0.43 (0.18, 1.02)	9	88.9	[U]1.99 (0.25, 15.98)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
[U]Unadjusted odds ratio; [a]Odds ratio adjusted for pre-operative periapical status

Occurrence of inter-appointment pain or swelling was associated with lower success rates for both types of treatment (Table 3.5.19). This effect on success rate was significant at the 5% level for primary root canal treatment cases only (Table 3.5.19); its prognostic value was retained after adjusting the results of analysis by pre-operative periapical status.

Systemic antibiotics were mostly prescribed by the referring dentists for management of inter-appointment pain or swelling in a small proportion (2.2% [25/1156] for primary root canal treatment; 0.7% [9/1311] for secondary root canal treatment) of the cases. Therefore its effect on the success of treatment was not investigated further.

viii) Root canal filling

The most commonly used root filling techniques during primary and secondary root canal treatment were lateral compaction of gutta-percha using cold spreader (23%, 22%), spreader warmed in a glass bead oven (28%, 31%) or an ultrasonically energized spreader (30%, 28%) (Table 3.5.20). They were followed by the warm vertical compaction technique, which was used in 14% of roots, regardless of treatment type. There was no significant difference in the success rates of treatment by these 4 commonly used techniques, regardless of treatment type (Table 3.5.20). This factor was therefore not investigated further.

The apical extent of root filling was initially analysed as a continuous variable and then as a categorical variable. The canal terminus was located by the electronic apex locator "0" reading position (verified by radiography and other aids); when judged to be accurate its location was recorded as 0 mm. The discrepancy between apical extent of root filling and the canal terminus was recorded as positive if the root filling was extruded into the periradicular tissue beyond the "0" reading point and as negative for those extending shorter than this reading within the canal. Root filling extents were categorized into "flush" (0–2mm short of the canal terminus), "short" (>2mm short of the canal terminus) and "long" (beyond the canal terminus) groups for statistical analyses and to allow comparison with the previous literature.

Table 3.5.20 Unadjusted and adjusted effects of intra-operative factors (root filling technique, extent and density) using logistic regression analysis

	Primary root canal treatment			Secondary root canal treatment		
Factors	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***	**No. of roots**	**Success rates (%)**	**Odds ratio (95% CI)***
Root filling technique			p = 0.8**			p = 0.06**
LC – Cold spreader (sp)	272	84.2	1	295	81.0	1
LC – Warm spreader	327	81.0	[U]0.80 (0.52, 1.23)	404	80.7	[U]0.98 (0.67, 1.43)
LC – U/S energized sp	347	83.6	[U]0.96 (0.62, 1.47)	365	78.4	[U]0.85 (0.58, 1.24)
Warm vertical compaction	160	83.8	[U]0.97 (0.57, 1.65)	189	81.5	[U]1.03 (0.65, 1.65)
Continuous wave	44	79.5	[U]0.73 (0.33, 1.63)	42	88.1	[U]1.73 (0.65, 4.62)
Obtura	14	71.4	[U]0.47 (0.14, 1.57)	15	53.3	[U]0.27 (0.09, 0.77)
MTA	2	100.0	Not analysed	4	75.0	[U]0.70 (0.07, 6.88)
Tagger hybrid	4	100.0	Not analysed	0	–	–
Apical extent of root filling[¥]			[U]p < 0.0001**			[U]p < 0.0001**
			[§]p < 0.0001**			[a]p < 0.0001**
Flush	954	85.8	1	1035	84.6	1
Short	70	74.3	[U]0.48 (0.27, 0.84)	162	64.8	[U]0.33 (0.23, 0.48)
			[a]0.48 (0.30, 0.78)			[a]0.35 (0.24, 0.50)
Long	146	67.1	[U]0.34 (0.23, 0.50)	117	61.5	[U]0.29 (0.19, 0.44)
			[a]0.50 (0.36, 0.70)			[a]0.39 (0.27, 0.58)
Voids within apical 5 mm of root filling						
No	1155	82.8	1	1307	80.3	1
Yes	15	86.7	[U]1.35 (0.30, 6.04)	7	42.9	[U]0.18 (0.04, 0.83)
			[a]1.15 (0.42, 3.15)			[a]0.28 (0.07, 1.09)
Extrusion of sealer						
No	865	84.2	1	942	81.1	1
Yes	305	79.0	[U]0.71 (0.51, 0.99)	372	77.7	[U]0.81 (0.60, 1.09)
			[a]0.81 (0.59, 1.12)			[a]1.03 (0.79, 1.35)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
[U]Unadjusted odds ratio; [a]Odds ratio adjusted for pre-operative periapical status
**P value of test for heterogeneity for categorical factor;
LC = lateral compaction technique

¥Flush = 0–2 mm from apex locator “0” reading position; Short = >2mm short of “0” reading position; Long = extruded beyond the “0” reading position

Roots with “flush” root fillings were associated with significantly higher success rates than “short” or “long” root fillings, regardless of treatment type (Table 3.5.20, page 177). The effect remained significant at the 5% level after adjusting for the pre-operative periapical status (Table 3.5.20). This factor was investigated further in the multiple regression models. The success rates of treatment by discrepancy between root filling and canal terminus are tabulated in table 3.5.21.

Table 3.5.21 Success rates of primary and secondary root canal treatment stratified by discrepancy between apical extent of root filling and canal terminus (EAL ‘0’)

		← Within canal																				EAL ‘0’	Long →									
	mm	**12.0**	**11.0**	**10.0**	**9.0**	**8.5**	**8.0**	**7.0**	**6.5**	**6.0**	**5.5**	**5.0**	**4.5**	**4.0**	**3.5**	**3.0**	**2.5**	**2.0**	**1.5**	**1.0**	**0.5**	**0.0**	**0.5**	**1.0**	**1.5**	**2.0**	**2.5**	**3.0**	**3.5**	**4.0**	**4.5**	**5.0**
1°RCT	**Total number of roots**	2	1	1	1	2	1	3	–	2	–	5	–	1	2	12	5	32	61	216	249	428	66	45	16	7	3	1	–	3	1	4
	Success rate (%)	50.0	100.0	0.0	100.0	100.0	100.0	33.3	–	100.0	–	100.0	–	100.0	100.0	66.7	40.0	81.3	85.2	89.4	85.1	84.6	72.7	64.4	68.8	42.9	66.7	0.0	–	0.0	100.0	100.0
2°RCT	**Total number of roots**	–	–	1	4	–	5	4	2	13	1	13	4	22	6	17	22	48	94	290	238	413	32	41	13	19	3	3	2	–	1	3
	Success rate (%)	–	–	100.0	50.0	–	60.0	50.0	50.0	53.8	0.0	53.8	75.0	63.6	50.0	76.5	68.2	70.8	80.9	86.2	87.4	82.8	71.9	56.1	53.8	63.2	66.7	66.7	0.0	–	100.0	66.7

1°RCT = primary root canal treatment; 2°RCT = secondary root canal treatment

The effect of “voids within the apical 5 mm of root filling” was initially found to have a significant association with success in secondary root canal treatment only. “Extrusion of sealer” was initially found to be significantly associated with lower success rates for primary root canal treatment. However both of these factors failed to retain prognostic value after the results of the analyses were adjusted for pre-operative periapical status (Table 3.5.20, page 177). Therefore these two factors were not investigated further.

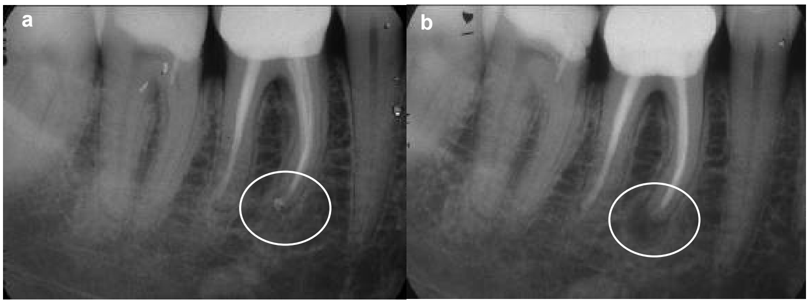
The absorption of the extruded sealer was assessed radiographically. Of the primary root canal treatment teeth, which on the immediate post-obturation radiograph showed evidence of extruded sealer (n=305), the final follow-up radiograph (taken at 2–4 years post-operatively) showed no signs of the extruded sealer in 39.0% (n=119), reduction in 59.0% (n=180) and no change in 2.0% (n=6).

Of the secondary root canal treatment teeth which on the immediate post-obturation radiograph showed evidence of extruded sealer (n=372), the final follow-up radiograph showed no signs of the extruded sealer in 64.8% (n=241), reduction in 32.0% (n=119) and no change in 3.2% (n=12).

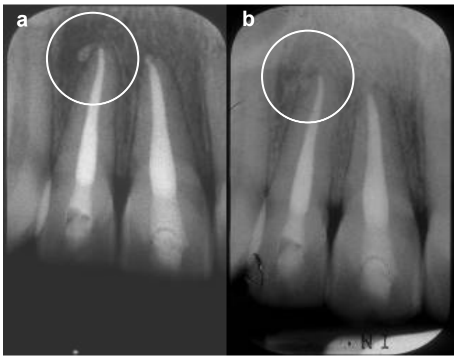
The difference in patterns of extruded sealer resorption after treatment for primary and secondary root canal treatment teeth was found to be statistically significant (P < 0.0001). Examples of the different patterns are presented below: cases with completely resorbed sealer (Figures 3.5.1a&b, 3.5.2a&b), partially resorbed sealer (Figure 3.5.3a&b), and unresorbed sealer (Figure 3.5.4a&b).

Figures 3.5.1a&b Example of extruded sealer from the distal root of a mandibular first molar (a) that was completely resorbed (b) at the time of follow-up

Figures 3.5.2a&b Example of extruded sealer from the mesial root of a mandibular first molar (a) that was completely resorbed (b) at the time of follow-up



Figures 3.5.3a&b Example of extruded sealer from a maxillary right lateral incisor (a) that was partially resorbed (b) at the time of follow-up



Figures 3.5.4a&b Example of extruded sealer from a maxillary canine (a) that remained the same (b) at the time of follow-up

3.5.2.5 Effects of post-operative restorative factors

Out of the six factors investigated, two (type of core material, type of core lining material) were initially found to have a significant association with the success of primary root canal treatment (Table 3.5.22 – Overleaf). Only "type of core lining" retained its prognostic value after adjusting for the pre-operative periapical status (Table 3.5.23 – Overleaf) and was investigated further in multiple logistic regression models.

Table 3.5.22 Unadjusted effects of post-operative restorative factors (provision, type, quality) using logistic regression analysis

	Primary root canal treatment			Secondary root canal treatment		
Factors	No. of roots	Success rates (%)	Odds ratio (95% CI)*	No. of roots	Success rates (%)	Odds ratio (95% CI)*
Who place the core material						
Referring dentist	113	85.8	1	273	76.6	1
Eastman Dental Hospital	1057	82.5	0.78 (0.45, 1.35)	1041	81.1	1.31 (0.95, 1.80)
Core material			P = 0.03**			P = 0.4**
Amalgam	769	84.9	1	874	81.5	1
Composite	221	75.1	0.54 (0.37, 0.77)	145	77.9	0.80 (0.52, 1.23)
Glass ionomer cement	83	88.0	1.30 (0.65, 2.58)	118	74.6	0.67 (0.43, 1.04)
IRM®	20	65.0	0.64 (0.33, 1.24)	27	70.4	0.73 (0.44, 1.22)
Post & amalgam	22	95.5	0.33 (0.13, 0.84)	57	87.7	0.54 (0.23, 1.26)
Cast post & core	55	78.2	3.73 (0.50, 28.0)	93	76.3	1.63 (0.72, 3.65)
Core lining used			P = 0.02**			P = 0.9**
None	630	84.3	1	732	80.6	1
GIC	81	69.1	0.42 (0.25, 0.70)	71	81.7	1.07 (0.57, 2.01)
IRM	459	83.2	0.92 (0.67, 1.28)	511	79.3	0.92 (0.69, 1.22)
Who made the final restoration						
Referring dentist	554	84.5	1	825	79.5	1
Eastman Dental Hospital	616	81.3	0.80 (0.59, 1.09)	489	81.2	1.11 (0.84, 1.48)
Type of restoration			P = 0.07**			P = 0.03**
GIC/Composite	265	75.8	1	165	73.3	1
Amalgam	207	83.6	1.62 (1.02, 2.57)	207	81.2	1.57 (0.96, 2.56)
Cast restoration	690	85.4	1.86 (1.31, 2.64)	923	81.6	1.61 (1.10, 2.36)
Temporary filling	8	75.0	0.96 (0.19, 4.85)	19	57.9	0.50 (0.19, 1.32)
Quality of restoration			P = 0.02**			P = 0.02**
Exposed root filling	15	40	1	8	37.5	1
Marginal defect	38	81.6	6.64 (1.78, 24.8)	69	69.6	3.81 (0.83, 17.43)
Satisfactory	1117	83.4	7.56 (2.66, 21.5)	1237	81.0	7.09 (1.68, 29.89)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor;

Table 3.5.23 Effects of 4 post-operative restorative factors adjusted for pre-operative periapical status using logistic regression analysis

	Primary root canal treatment	Secondary root canal treatment
Factors	Adjusted odds ratio (95% CI)*	Adjusted odds ratio (95% CI)*
Core material	p = 0.2**	
Amalgam	1	Not analysed (*no prognostic value from initial analysis*)
Composite	0.71 (0.47, 1.06)	
GIC	1.19 (0.54, 2.64)	
IRM®	0.49 (0.11, 2.16)	
Stainless steel post & amalgam	5.02 (0.72, 35.03)	
Cast post & core	0.74 (0.33, 1.67)	
Core lining used	P = 0.1**	
No	1	Not analysed (*no prognostic value from initial analysis*)
GIC	0.50 (0.28, 0.89)	
IRM	0.96 (0.64, 1.42)	
Type of restoration	P = 0.5**	P = 0.04**
GIC/Composite	1	1
Amalgam	1.32 (0.75, 2.31)	1.36 (0.71, 2.61)
Cast restoration	1.39 (0.93, 2.08)	1.45 (0.96, 2.21)
Temporary filling	1.37 (0.15, 12.63)	0.38 (0.12, 1.20)
Quality of restoration	P = 0.01**	P = 0.03**
Exposed root filling	1	1
Marginal defect	7.62 (1.34, 43.30)	5.23 (0.95, 28.77)
Satisfactory	7.34 (1.69, 32.00)	8.43 (1.72, 41.38)

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor;

Another two factors (type of coronal restoration, quality of restoration) were initially found to have significant association with the success of primary and secondary root canal treatment (Table 3.5.22, page 180). The former failed to retain its prognostic value for primary root canal treatment after the results were adjusted for the pre-operative periapical status (Table 3.5.23, page 180). The direction and magnitude of the effect of quality of restoration on the success of primary and secondary root canal treatment remained the same even after the results were adjusted for the pre-operative periapical status (Table 3.5.23). These two factors were therefore investigated further in multiple logistic regression models.

3.5.2.6 Summary of potential prognostic factors identified for further analyses

In summary, fifteen potential prognostic factors for primary root canal treatment and seventeen for secondary root canal treatment were identified (Table 3.5.24). Seven of the factors were common for the two types of treatment.

Table 3.5.24 Potential significant prognostic factors for primary and secondary root canal treatment

Potential significant factors for primary root canal treatment only	Common potential significant factors	Potential significant factors for secondary root canal treatment only
1. Pre-operative pulpal status* 2. Pre-operative periodontal probing depth 3. Apical size of canal preparation 4. Taper of canal preparation 5. Additional use of CHX as irrigant 6. Inter-appointment pain 7. Inter-appointment swelling 8. Type of core lining material	1. Root type 2. Pre-operative sinus 3. Pre-operative periapical status 4. Size of periapical lesion 5. Apical extent of instrumentation 6. Apical extent of root filling 7. Quality of restoration	1. Pre-operative swelling 2. Pre-operative root perforation** 3. Type of pre-operative foreign material** 4. Type of pre-operative fractured instrument** 5. Fate of pre-operative foreign material** 6. Type of instrument for canal preparation 7. Patency at apical foramen 8. Intra-operative canal perforation 9. Canal blockage during treatment 10. Additional use of EDTA as irrigant

*Factor was not applicable to secondary root canal treatment; **Factors were not applicable to primary root canal treatment

Each of the above potential prognostic factors was entered simultaneously into a multiple logistic regression model with pre-operative periapical status and size of lesion as covariates. There were 10 and 11 factors for primary and secondary root canal treatment that reached statistical significance at the 5% level or had a large effect but only significant at the 10% level, respectively (Table 3.5.25 – Overleaf).

Table 3.5.25 Factors found to have prognostic value after adjusting for pre-operative status and size of lesion

Primary root canal treatment	Secondary root canal treatment
1. Pre-operative pulpal status; 2. Pre-operative periodontal probing depth; 3. Pre-operative sinus; 4. Apical extent of instrumentation; 5. Apical size of canal preparation (≤30, >30); 6. Additional use of CHX for irrigation; 7. Inter-appointment pain; 8. Inter-appointment swelling; 9. Apical extent of root filling; and 10. Quality of restoration.	1. Pre-operative sinus; 2. Pre-operative swelling; 3. Fate of pre-operative foreign material; 4. Pre-operative perforation; 5. Patency at apical foramen; 6. Apical extent of instrumentation; 7. Intra-operative canal perforation; 8. Intra-operative canal blockage; 9. Additional use of EDTA for irrigation; 10. Apical extent of root filling; and 11. Quality of restoration.

Of the potential prognostic factors influencing the success of secondary root canal treatment (Table 3.5.25), only one factor (fate of pre-operative foreign material) was unique to secondary root canal treatment. Clinically, the "fate of pre-operative foreign material" was a surrogate measure for the ability to clean or fill the canal to the apical terminus. "Fate of pre-operative foreign material" was therefore not investigated further.

Considering that all the remaining potential prognostic factors were common to both types of treatment (except pre-operative pulpal status), it was decided to combine the two datasets in order to increase the statistical power for further analyses. For the "pre-operative pulpal status", an additional category (previously treated) was added to record those roots that had undergone secondary root canal treatment. An additional binary variable (type of treatment: primary, secondary) was also generated to distinguish between roots undergoing primary and secondary root canal treatment. The interactions between "type of treatment" and other potential factors (shown in previous analyses to have different effects on primary and secondary root canal treatment) were investigated further.

3.5.3 Final multiple logistic regression model building using the combined dataset

All the analyses in this section were carried out using a logistic regression model that allowed for the clustering effect by patient. Initially, each of the factors with prognostic values (Table 3.5.25) was entered simultaneously with "pre-operative periapical status" and "size of periapical lesion" into a multiple logistic regression model (Table 3.5.26 – Overleaf). All except two factors (pre-operative pulpal status, apical size of canal preparation) retained their prognostic value (Table 3.5.26).

Table 3.5.26 Multiple logistic regression models incorporating pre-operative periapical status and size of pre-operative lesion together with each of the other potential factors as predictors

Factors	Odds ratio (OR)	*95% CI for OR	P value
Type of treatment			
Primary root canal treatment	1		
Secondary root canal treatment	0.78	0.61, 1.01	0.06
Pre-operative pulpal status			
Non-vital	1		
Vital	1.39	0.83, 2.35	0.2
Retreat	0.82	0.63, 1.06	0.1
Pre-operative sinus			
No	1		
Yes	0.49	0.34, 0.71	<0.001
Periodontal probing depth			
<5mm	1		
≥5mm	0.35	0.12, 1.01	0.05
Pre-operative swelling			
No	1		
Yes	0.70	0.48, 1.02	0.06
Pre-operative perforation			
No	1		
Yes	0.38	0.17, 0.87	0.02
Patency at apical foramen			
No	1		
Yes	2.19	1.55, 3.08	<0.001
Apical extent of intrumentation			
Continuous variable	0.84	0.78, 0.91	<0.001
Apical size of canal preparation			
Continuous variable	1.00	0.99, 1.00	0.80
Intra-operative canal perforation			
No	1		
Yes	0.60	0.40, 0.91	0.02
Intra-operative canal blockage			
No	1		
Yes	0.57	0.31, 1.07	0.08
Additional use of CHX as irrigant			
No	1		
Yes	0.65	0.42, 1.02	0.06
Additional use of EDTA as irrigant			
No	1		
Yes	1.46	1.08, 1.97	0.02
Intra-appointment pain			
No	1		
Yes	0.65	0.46, 0.93	0.02
Intra-appointment swelling			
No	1		
Yes	0.47	0.25, 0.89	0.02
Apical extent of root filling			
Flush	1		
Short	0.37	0.28, 0.50	<0.001
Long	0.45	0.35, 0.59	<0.001
Quality of restoration			
Exposed root filling	1		
Marginal defect	5.92	1.77, 19.85	0.004
Satisfactory	8.38	2.8, 25.08	<0.001

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients

In all the following analyses, three variables (type of treatment, pre-operative periapical status, size of periapical lesion) were kept in all multiple regression models. Although “type of treatment” only reached significance at the 10% level in the previous analysis, it was kept in the model to investigate its potential interaction with other prognostic factors. Pain and swelling are likely to occur concomitantly during inter-appointment flare-up. Thus these two factors: inter-appointment pain and inter-appointment swelling were combined for analyses in the following multiple regression models.

In model 1 (Table 3.5.27), all the 4 potential pre-operative prognostic factors were entered simultaneously with the above three variables. Two factors; “pre-operative swelling” and “pre-operative periodontal probing depth” failed to retain their prognostic value.

Table 3.5.27 Multiple logistic regression model incorporating pre-operative periapical status, size of pre-operative lesion & type of treatment together with other potential pre-operative factors as predictors

Model 1			
Factors	**OR**	***95% CI for OR**	**P value**
Type of treatment			
Primary root canal treatment	1		
Secondary root canal treatment	0.78	0.60, 1.01	0.06
Periapical status			
Intact periodontal ligament	1		
Widened periodontal ligament	0.79	0.57, 1.07	0.1
Periapical lesion	0.50	0.37, 0.67	<0.001
Size of periapical lesion			
Continuous variable	0.88	0.84, 0.92	<0.001
Pre-operative sinus			
No	1		
Yes	0.51	0.34, 0.76	0.001
Pre-operative periodontal probing depth>5mm			
No	1		
Yes	0.85	0.64, 1.14	0.3
Pre-operative swelling			
No	1		
Yes	0.95	0.63, 1.45	0.8
Pre-operative perforation			
No	1		
Yes	0.44	0.21, 0.95	0.04

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients

In model 2 (Table 3.5.28 – Overleaf), all the 7 potential intra-operative prognostic factors were entered into Model 1 after removing those pre-operative factors which lost their prognostic values.

“Apical extent of instrumentation” and “Apical extent of root filling” were significantly correlated (P < 0.001). It was as expected, because it is normal practice to place the root filling to the full length of the prepared canal. On the other hand “apical extent of root filling” might be measuring some other aspect of treatment or pre-operative condition additional to “apical extent of instrumentation”. In order to include both factors simultaneously into the same model, “apical extent of root filling” was converted into a binary variable (Long root filling) to measure the extrusion of root filling material into the periapical tissues.

The results of the analysis (Table 3.5.28) revealed that the “type of treatment” and “pre-operative perforation” failed to reach significance at the 10% and 5% levels, respectively. Of the intra-operative factors, “intra-operative perforation” also failed to reach significance at the 5% level. In the subsequent analyses, “pre-operative perforation” and “intra-operative perforation” were combined into one variable as “pre- or intra-operative perforation” as they were significantly (P < 0.001) correlated with each other.

Table 3.5.28 Multiple logistic regression model incorporating pre-operative periapical status, size of pre-operative lesion & type of treatment, the other 2 significant pre-operative factors together with all the 7 potential intra-operative factors as predictors

Model 2			
Factors	**OR**	***95% CI for OR**	**P value**
Periapical status			
Intact periodontal ligament	1		
Widened periodontal ligament	0.74	0.54, 1.03	0.07
Periapical lesion	0.46	0.34, 0.63	<0.001
Size of periapical lesion			
Continuous variable	0.88	0.84, 0.92	<0.001
Type of treatment			
Primary root canal treatment	1		
Secondary root canal treatment	0.83	0.64, 1.09	0.2
Pre-operative sinus			
No	1		
Yes	0.51	0.35, 0.73	<.001
Pre-operative perforation			
No	1		
Yes	0.48	0.21, 1.08	0.08
Patency at canal terminus			
No	1		
Yes	1.79	1.18, 2.72	0.006
Apical extent of instrumentation			
Continuous variable	0.89	0.81, 0.98	0.02
Long root filling			
No	1		
Yes	0.47	0.35, 0.61	<0.001
Intra-operative perforation			
No	1		
Yes	0.67	0.44, 1.03	0.07
Additional use of CHX as irrigant			
No	1		
Yes	0.57	0.35, 0.93	0.03
Additional use of EDTA as irrigant			
No	1		
Yes	1.56	1.12, 2.17	0.009
Inter-appointment pain or swelling			
No	1		
Yes	0.55	0.38, 0.77	0.001

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients

In model 3 (Table 3.5.29 – Overleaf), the “quality of restoration” was entered into Model 2 (Table 3.5.28) after removing those factors which lost their prognostic values. As the effect of “additional use of EDTA as irrigant” was found to have different effects on the primary and secondary root canal treatment when the two datasets were analysed separately, an interaction term “type of treatment*EDTA” was incorporated in the model to explore this potential interaction.

Table 3.5.29 Final multiple logistic regression model incorporating pre-operative periapical status, size of pre-operative lesion, type of treatment, the other 2 significant pre-operative factors, 6 significant intra-operative factors together with the quality of restoration as predictors

Model 3			
Factors	**OR**	***95% CI for OR**	**P value**
Type of treatment			
Primary root canal treatment	1		
Secondary root canal treatment	0.78	0.55, 1.10	0.2
Periapical status			
Intact periodontal ligament	1		
Widened periodontal ligament	0.86	0.52, 1.42	0.5
Periapical lesion	0.51	0.32, 0.80	0.003
Size of periapical lesion			
Continuous variable	0.86	0.81, 0.91	<0.001
Pre-operative sinus			
No	1		
Yes	0.53	0.36, 0.77	0.001
Pre- or intra-operative perforation			
No	1		
Yes	0.46	0.21, 1.02	0.06
Patency at canal terminus			
No	1		
Yes	2.22	1.38, 3.59	0.001
Apical extent of instrumentation			
Continuous variable	0.87	0.79, 0.97	0.01
Long root filling			
No	1		
Yes	0.38	0.27, 0.54	<0.001
Additional use of CHX as irrigant			
No	1		
Yes	0.47	0.26, 0.83	0.01
Type of treatment* EDTA			
No	1		
Yes	1.81	0.90, 3.64	0.09
Additional use of EDTA as irrigant			
Primary root canal treatment			
No	1		
Yes	1.26	0.76, 2.09	0.4
Secondary root canal treatment			
No	1		
Yes	2.28	1.37, 3.81	0.002
Inter-appointment pain or swelling			
No	1		
Yes	0.53	0.36, 0.79	0.002
Quality of restoration			
Exposed root filling	1		
Marginal defect	7.69	2.28, 25.95	0.001
Satisfactory	10.73	3.65, 31.54	<0.001

*Confidence interval for odds ratio estimated using robust standard error to allow for clustering within patients

In this model (Table 3.5.29), all the factors incorporated, with the exception of three factors: “type of treatment”, “pre- or intra-operative perforation”, “interaction between type of treatment and additional use of EDTA”, reached statistical significance at the 5% level. The type treatment failed to reach significance at the 10% level, but the other two factors did. This model was therefore adopted as the final model to describe the prognostic factors for primary and secondary root canal treatment.

The goodness-of-fit tests from Deviance statistic and Pearson chi squared statistic, divided by residual degree of freedom, were both close to one, 0.83 and 0.99 respectively. This indicated that there was no evidence of over-dispersion in the final model. The fit of the final model was also assessed using Hosmer-Lemeshow goodness-of-fit test (Hosmer & Lemeshow 1988) which did not detect lack of fit (Hosmer-Lemeshow X^2 5.33 [8df], P = 0.72). Consequently, the final logistic regression model was considered appropriate.

3.5.4 Summary of results

The probabilities of success measured by absence of apical periodontitis were 82.8% (n = 969) and 80.1% (n = 1043) for primary and secondary root canal treatment, respectively. The difference (2.7%) was however, not significant (P = 0.2).

Four pre-operative factors, six intra-operative factors and one post-operative factor were found to be significant prognostic indicators for the success of primary and secondary root canal treatment.

Those roots with a pre-operative periapical lesion were significantly associated with 49% lower odds of success (OR = 0.51, 95% CI 0.32, 0.80) than roots without a lesion. The odds of success of treatment was found to decrease by 14% for every 1 mm increase in the diameter of the pre-operative lesion (OR = 0.86, 95% CI 0.81, 0.91). The presence of a pre-operative sinus (OR = 0.52, 95% CI 0.36, 0.77) or root perforation (OR = 0.44, 95% CI 0.21, 1.02) significantly reduced the odds of success by 48% and 56%, respectively.

During treatment, achieving patency at the canal terminus significantly increased the odds of success by 2-fold (OR 2.22, 95% CI 1.37, 3.59). Whereas, the odds of success was reduced by 12% (OR = 0.88, 95% CI 0.79, 0.97) for every 1 mm of the canal short of the terminus that remained “un-instrumented”. In contrast, a long root filling reduced the odds of success by 62% (OR = 0.38, 95% CI 0.27, 0.54). The use of Corsodyl® in addition to sodium hypochlorite solution for canal irrigation did not improve but reduced the odds of success by 53% (OR = 0.47; 95% CI 0.27, 0.83). Interestingly, the additional use of EDTA solution for canal irrigation had no significant effect (OR = 1.26, 95% CI 0.76, 2.09) on the success of primary root canal treatment but significantly increased the odds of success of secondary root canal treatment by 2-fold (OR = 2.28, 95% CI 1.37, 3.81). The occurrence of inter-appointment complications (swelling or pain) reduced the odds of success by 47% (OR = 0.53; 95% CI 0.36, 0.79).

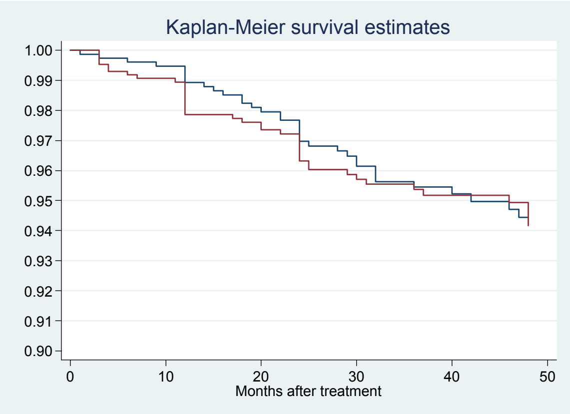
Finally, a good quality coronal restoration significantly increased the odds of success by 11-fold (OR = 10.73, 95% CI 3.65, 31.54).

3.6 Results of investigation of tooth survival after primary or secondary root canal treatment

3.6.1 Probabilities of tooth survival

By the end of the study period, 95.4% (95% CI 93.6%, 96.8%) (724/759) of the teeth undergone primary root canal treatment and 95.2% (95% CI 93.6%, 96.5%) (817/858) of the teeth having undergone secondary root canal treatment were present at their follow-up review (Figure 3.6.1). The hazard of tooth loss after secondary root canal treatment was slightly higher than that after primary root canal treatment within the first year after treatment but there was no obvious difference after 1 year (Figure 3.6.1). Preliminary univariable Cox regression analysis revealed the overall difference in hazard of tooth loss after primary or secondary root canal treatment was not significant at the 5% level (HR = 1.07; 95% CI 0.68, 1.70).

Figure 3.6.1 Kaplan-Meier survival estimates by primary (blue line) and secondary (red line) root canal treatment



Tooth loss by extraction occurred between 1–47 months and 3–48 months after primary and secondary root canal treatment, respectively. Most of the lost teeth were extracted within 2 years after treatment (Table 3.6.1).

Table 3.6.1 Time of tooth extraction after treatment

	Within 1 year	1-2 years	2-3 years	3-4 years
Primary root canal treatment	8 (22.8%)	14 (40.0%)	9 (25.7%)	4 (11.4%)
Secondary root canal treatment	18 (43.7%)	12 (29.3%)	6 (14.6%)	5 (12.2%)

The reasons for tooth extraction could be classified into 5 groups (Table 3.6.2 – Overleaf). The trends were the same for both primary and secondary root canal treatment; the respective figures are given in brackets in the following summary. The most common set of reasons were classified under endodontic problems (28.6%, 39.0%), followed by tooth or root facture (28.6%, 29.3%), restoration failure (22.9%, 22.0%), and restorative or orthodontic treatment plan (14.3%, 9.7%).

Table 3.6.2 Reasons for tooth extraction after primary (1^{o}RCT) or secondary (2^{o}RCT) root canal treatment

Reasons	1^{o}RCT (n = 35)	2^{o}RCT (n = 41)
Endodontic problem		
Pain	3	6 (1 root fracture)
Pain (chronic pain problem)	0	1
Pain & swelling	2 (1 periodontal problem)	3
Pain after crown placement by GDP	1	0
Sinus	2	3
Sinus & pain	1	0
Sinus & swelling	1	0
Sinus & tooth facture	0	2 (1 tooth fracture, 1 tooth & root fracture)
Swelling	0	1
Subtotal	**10 (28.6%)**	**16 (39.0%)**
Tooth / root fracture		
Root fracture	1	1
Tooth and root fracture (vertical)	0	1
Tooth fracture	9 (2 bruxers, 1 clencher)	10 (1 was bridge abutment, 1 replaced with implant)
Subtotal	**10 (28.6%)**	**12 (29.3%)**
Restoration failure		
Bridge failure	0	2
Bridge fracture	2 (1 was abutment, 1 replaced with implant)	0
Crown failure (tooth unrestorable)	5	6 (1 replaced with implant)
Plastic restoration failure	0	1
Post perforation & fracture	1	0
Subtotal	**8 (22.9%)**	**9 (22.0%)**
Restorative or orthodontic treatment plan		
Aesthetic denture	0	1
Implant treatment	4	3
Orthodontic treatment plan	1	0
Subtotal	**5 (14.3%)**	**4 (9.7%)**
Periodontal problem		
	1	0
Subtotal	**1 (2.8%)**	**0 (0.0%)**
Other		
Worry about Hg poisoning	1	0
Subtotal	**1 (2.8%)**	**0 (0%)**
Total	**35 (100%)**	**41 (100%)**

3.6.2 Identification of prognostic factors predicting using survival regression analyses

Sections 3.6.2.1 to 3.6.2.5 present the results of Cox survival regression analyses on the effect of each potential prognostic factor that was adjusted for the type of treatment using the combined dataset. The clustering effect within patients was accounted for in all the models.

3.6.2.1 General patient and tooth factors

i) Patient factors

The hazard of tooth loss increased slightly (2%) with the passing of each year but the difference was not significant at the 10% level (Table 3.6.3). There was no obvious difference in the rate of post-treatment tooth loss between male and female patients (Table 3.6.3).

Table 3.6.3 Effects of each patient characteristic adjusted for type of treatment using Cox regression analysis

	1°RCT		2°RCT		
Patient characteristics	**No. of teeth**	**Loss (%)**	**No. of teeth**	**Loss (%)**	**HR adjusted for type of treatment (95% CI)***
Age (continuous data)	–	–	–	–	1.02 (0.10, 1.03)
Sex					
Female	441	5.2	552	4.2	1
Male	318	3.8	306	5.9	1.06 (0.64, 1.74)
Diabetic					
No	737	3.9	835	4.8	1
Yes	22	27.3	23	4.4	3.65 (1.43, 9.29)
Allergic					
No	588	4.1	654	4.7	1
Yes	171	6.4	204	4.9	1.21 (0.70, 2.09)
Systemic steroid					
No	748	4.7	846	4.5	1
Yes	11	0.0	12	25.0	2.80 (0.96, 9.09)
Long term antibiotics					
No	752	4.7	852	4.8	
Yes	7	0.0	6	0.0	Not analysed
Thyroxin therapy					
No	733	4.5	831	4.5	1
Yes	26	7.7	27	14.8	2.53 (1.01, 6.39)
Hormone replacement					
No	727	4.8	837	4.8	1
Yes	32	0.0	21	4.8	0.38 (0.05, 2.78)
Coronary heart disease					
No	701	4.3	801	4.6	1
Yes	58	8.6	57	7.0	1.08 (0.68, 1.71)

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients

Amongst the impact of medical conditions analysed (Table 3.6.3), diabetes, systemic steroid therapy, thyroxin therapy were found to be significantly ($P < 0.1$) associated with a higher hazard of tooth loss after treatment. These conditions were therefore analysed further in multiple regression models.

ii) Tooth morphological type and developmental anomaly

Maxillary premolars were associated with the highest hazard of tooth loss and the result was significant at the 10% level (Table 3.6.4 – Overleaf). It was followed by mandibular molars but the difference was not significant (Table 3.6.4).

All the teeth with developmental anomalies survived within the study period but the sample size was very small (Table 3.6.4).

Table 3.6.4 Effects of tooth type and developmental anomaly adjusted for type of treatment using Cox regression analysis

	1°RCT		2°RCT		
Factors	**No. of teeth**	**Loss (%)**	**No. of teeth**	**Loss (%)**	**HR adjusted for type of treatment (95% CI)***
Tooth type					P = 0.1**
Maxillary incisors/canine	219	4.6	149	2.7	1
Maxillary premolars	71	9.9	121	6.6	2.02 (0.90, 4.54)
Maxillary molars	156	3.9	186	3.2	0.93 (0.40, 2.18)
Mandibular incisors/canine	74	1.3	68	2.9	0.56 (0.16, 1.96)
Mandibular premolars	40	0.0	54	5.6	0.82 (0.23, 2.95)
Mandibular molars	199	5.5	280	6.4	1.64 (0.82, 3.25)
Developmental anomalies					
No	748	4.7	857	4.8	
Yes	11	0.0	1	0.0	Not analysed

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor

The prevalence of post-operative tooth fracture as the cause of extraction was explored by tooth type. Interestingly, 60% (9/15) of the extracted maxillary premolars had suffered fractured, followed by mandibular incisors (33%, 1/3), maxillary molars (17%, 2/12) and mandibular molars (17%, 9/54). None of the extracted maxillary incisors/canines and mandibular premolars had been fractured. The most common reason for extraction of maxillary incisors/canines after treatment was related to implant placement in the adjacent sites (36%, 5/14). Two of the three mandibular premolars were extracted because of failure of the coronal restoration, after which the tooth was deemed unrestorable.

3.6.2.2 Pre-operative factors

i) Pre-operative tooth characteristics common for both primary and secondary root canal treatment

Out of the 14 possible prognostic factors investigated, 4 factors (pre-operative pain, pre-operative sinus, pre-operative periodontal probing depth, pre-operative cervical resorption) were found to have a significant association with the hazard of tooth loss after treatment at the 5% level (Table 3.6.5 – Overleaf).

The presence of pre-operative pain was associated with a greater than 2-fold higher hazard of tooth loss (HR = 2.21; 95% CI 1.34, 3.62). The hazard of tooth loss was 2.6 times higher in teeth with pre-operative sinus than those without (HR = 2.60; 95% CI 1.54, 4.40). Similarly, teeth with deeper than 5 mm periodontal probing depths pre-operatively were associated with 2.4 times (HR = 2.39; 95% CI 0.95, 6.03) higher hazard of tooth loss after treatment. These three factors were therefore investigated further in multiple regression models.

Teeth with pre-operative cervical resorption were associated with a significantly higher hazard of tooth loss (HR = 4.48; 95% CI 1.28, 15.78) after treatment; therefore this factor was analysed in multiple regression models.

Table 3.6.5 Effects of pre-operative factors adjusted for type of treatment using Cox regression analysis

	1^{o}RCT		2^{o}RCT		
Factors	**No. of teeth**	**Loss (%)**	**No. of teeth**	**Loss (%)**	**HR adjusted for type of treatment (95% CI)***
History of luxation injuries					
No	589	4.9	792	5.1	1
Yes	170	3.5	66	1.5	0.60 (0.25, 1.41)
History of fracture or crack					P = 0.7**
No	597	3.9	724	5.3	1
Fracture	98	9.2	71	1.4	1.36 (0.64, 2.89)
Cracks	64	4.7	63	3.2	0.92 (0.37, 2.31)
Restoration type					P = 0.9**
Virgin tooth	179	3.4	-	-	0.72 (0.26, 1.98)
Plastic restoration	272	4.4	428	4.9	1
Plastic + post	-	-	6	0.0	-
Cast restoration	163	4.9	245	4.5	0.95 (0.54, 1.67)
Cast restoration + post	9	11.1	52	5.8	1.47 (0.51, 4.24)
Temporary dressing	120	5.8	112	4.5	1.26 (0.65, 2.41)
Open cavity	16	6.3	15	6.7	1.02 (0.62, 1.67)
Pain					
No	445	2.9	493	3.5	1
Yes	314	7.0	365	6.6	2.21 (1.34, 3.62)
Tenderness to percussion					
No	459	3.9	464	4.1	1
Yes	300	5.7	394	5.6	1.47 (0.92, 2.34)
Soft tissue tenderness					
No	543	3.9	568	4.8	1
Yes	216	6.5	290	4.8	1.32 (0.81, 2.13)
Soft tissue swelling					
No	678	4.4	770	4.7	1
Yes	81	6.2	88	5.7	1.32 (0.67, 2.60)
Sinus					
No	661	4.1	761	3.9	1
Yes	98	8.2	97	11.3	2.60 (1.54, 4.40)
Periodontal probing depth ≥5mm					
No	735	4.5	836	4.6	1
Yes	24	8.3	22	13.6	2.39 (0.95, 6.03)
Pulpal status					
Non-vital	613	4.6	–	–	1
Vital	146	4.8	858	4.8	1.07 (0.47, 2.43)
Periapical status					P = 1.0**
Intact PDL	157	3.8	125	6.4	1
Widened PDL	99	5.1	96	4.2	0.95 (0.40, 2.24)
Periapical lesion	503	4.8	637	4.6	0.95 (0.51, 1.76)
Size of periapical lesion					
Continuous variable	–	–	–	–	1.05 (0.98, 1.13)
Root resorption					P = 0.03**
No	663	4.7	787	5.1	1
Internal	19	0	8	0.0	Not analysed
External (apical)	56	3.6	60	1.7	0.52 (0.16, 1.66)
External (lateral)	10	0	3	0.0	Not analysed
Internal & external apical	2	0	–	–	Not analysed
Cervical	9	22.2	–	–	4.48 (1.28, 15.78)
Perforation					P = 0.4**
No	745	4.4	832	4.7	1
Apical/mid-root level	–	–	4	0.0	Not analysed
Coronal (Sub-osseous)	3	33.3	10	10.0	3.23 (0.77, 13.49)
Coronal (Supra-osseous)	11	9.1	12	8.3	1.87 (0.45, 7.77)
Coronal	*14*	*4.6*	*22*	*9.1*	*2.37 (0.85, 6.59)*

PDL = Periodontal ligament space
*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor

Teeth with pre-operative perforations in the crown above or below bone levels, were associated with a substantially higher hazard of tooth loss than those without (Table 3.6.5, page 192). However, the differences were not statistically significant at the 10% level. The two types of coronal perforation (sub-osseous, supra-osseous) were combined for further analysis. The results showed that the presence of perforation at the coronal level was associated with a significantly higher hazard (HR = 2.37; 95% CI 0.85, 6.59) of tooth loss at the 10% level (Table 3.6.5), therefore this factor was investigated further in multiple regression models.

ii) <u>Pre-operative tooth factors unique to secondary root canal treatment</u>

The effects of these factors were investigated using data for teeth having undergone secondary root canal treatment (Table 3.6.6).

Table 3.6.6 Unadjusted effects of pre-operative factors unique to secondary root canal treatment using Cox regression analysis

	2^{o}RCT		
Factors	**No. of teeth**	**Loss (%)**	**Unadjusted HR (95% CI)***
Satisfactory root filling			
No	145	6.9	1
Yes	713	4.4	1.50 (0.73, 3.09)
Canal content			
Un-instrumented	0	0.0	
Empty but instrumented	3	33.3	Not analysed
Foreign material	855	4.7	
Type of foreign material			P = 0.03**
$Ca(OH)_2$	7	1.1	0.61 (0.08, 4.69)
Gutta-percha	660	4.2	1
Cement	31	7.4	1.74 (0.42, 7.21)
Thermafil	6	0.0	Not analysed
Silver point	46	2.5	0.57 (0.08, 4.14)
Fractured instrument	105	11.4	2.94 (1.47, 5.93)
Presence of fractured instrument			
No	753	3.9	1
Yes	105	11.4	3.13 (1.62, 6.05)
Fate of foreign material			P < 0.0001**
Remained the same	56	16.1	1
Bypassed	25	4.0	0.26 (0.03, 2.12)
Removed	761	3.9	0.25 (0.12, 0.51)
Extruded apically	13	0.0	Not analysed

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor

Out of five prognostic factors, two (presence of fractured instruments, fate of foreign material) were found to have a significant (P < 0.05) association with the hazard of tooth loss after secondary root canal treatment (Table 3.6.7 – Overleaf). These two factors were therefore further investigated in multiple regression models using the secondary root canal treatment dataset.

3.6.2.3 Operator's qualification & prediction of prognosis and treatment visits.

When comparing the rate of tooth loss by operator's experience, those treatments carried out by 2nd year postgraduate students were associated with a lower hazard of tooth loss than those performed by 1st year postgraduate students (Table 3.6.7). On the other hand, treatment carried out by staff members were associated with a higher hazard of tooth loss than treatment carried out by 1st year postgraduate students (Table 3.6.7). As these differences were not significant at the 10% level, the operator's experience was not analysed further.

Table 3.6.7 Effects of operator's qualification & number of treatment visits adjusted for type of treatment using Cox regression analysis

	1^{o}RCT		2^{o}RCT		
Factors	**No. of teeth**	**Loss (%)**	**No. of teeth**	**Loss (%)**	**HR adjusted for type of treatment (95% CI)***
Operator's experience					P = 0.3**
1st year students	474	5.1	543	5.2	1
2nd year students	215	4.2	243	2.5	0.63 (0.32, 1.23)
Staff member	70	2.9	72	9.7	1.22 (0.59, 2.50)
Number of treatment visits					
1	12	8.3	4	0	
2	326	2.5	321	3.7	
3	255	5.5	294	4.1	
7	96	6.3	157	7.1	
5	48	12.5	50	8.0	Not analysed
6	13	0	21	4.8	
7	8	0	5	0	
8	–	–	1	16.7	
9	1	0	–	–	

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients
**P value of test for heterogeneity for categorical factor

The proportion of teeth lost by number of treatment visits for primary and secondary root canal treatment is presented in table 3.6.7. However, its effect on tooth loss was not analysed because it was not possible to account for many potential hidden confounders including the reasons for the requirement of additional visits.

3.6.2.4 Intra-operative factors

Out of the 15 intra-operative factors investigated, 4 (patent at apical foramen, blockage of canal, crown or root perforation, extrusion of root filling) were found to have prognostic value for tooth loss (Table 3.6.8 – Overleaf).

If patency at the apical terminus could be achieved in any root during treatment, the hazard of tooth loss was significantly ($P < 0.1$) reduced by 51% (HR = 0.49; 95% CI 0.24, 1.01) (Table 3.6.8). In contrast, presence of canal blockage in other roots or subsequent blockage of initially patent canals during instrumentation significantly ($P < 0.05$) increased the hazard of tooth loss by 77% (HR = 1.77; 1.03, 3.03) (Table 3.6.8).

Table 3.6.8 Effects of intra-operative factors adjusted for type of treatment using Cox regression analysis

	1°RCT			2°RCT			
Factors	**No. of teeth**	**Loss (%)**		**No. of teeth**	**Loss (%)**		**HR adjusted for type of treatment (95% CI)***
Protect the tooth with a band							
No	604	4.2		681	5.0		1
Yes	155	5.8		177	4.0		1.06 (0.59, 1.90)
Use of magnification							
No	620	4.8		530	4.3		1
Yes	139	3.6		328	5.5		1.14 (0.70, 1.87)
Patency at canal terminus							
No	39	10.3		70	7.1		1
yes	720	4.3		788	4.6		0.49 (0.24, 1.01)
Blockage of canal							
No	687	4.5		685	4.1		1
Yes	72	5.6		173	7.5		1.77 (1.03, 3.03)
Perforation							
No	728	4.3		848	4.5		1
Yes	31	12.9		10	20.0		2.04 (1.33, 3.13)
Fractured of instrument							
No	745	4.7		842	4.8		1
Yes	14	0.0		16	6.3		1.45 (0.16, 13.53)
NaOCl concentration							
2.5%	533	4.1		790	4.9		1
4–5%	226	5.8		68	2.9		0.57 (0.18, 1.83)
Irrigation solution							
NaOCl alone	533	4.1		493	5.9		1
NaOCl combined + other*	226	5.8		365	3.3		0.88 (0.52, 1.51)
Additional use of iodine							
No	695	4.9		666	5.3		1
Yes	64	1.6		192	3.1		0.52 (0.24, 1.15)
Additional use of CHX							
No	728	4.7		771	5.1		1
Yes	31	3.2		87	2.3		0.57 (0.18, 1.85)
Additional use of EDTA							
No	572	4.0		630	4.8		1
Yes	187	6.4		228	4.8		1.34 (0.79, 2.27)
Inter-appointment pain							
No	724	3.9		724	4.8		1
Yes	85	9.4		134	4.5		1.48 (0.80, 2.75)
Inter-appointment swelling							
No	736	4.5		835	4.8		1
Yes	23	4.4		23	4.3		0.92 (0.22, 3.86)
Extrusion of root filling							
No	646	3.7		758	4.6		1
Yes	113	9.7		100	6.0		1.85 (1.10, 3.10)
Extrusion of sealer							
No	508	4.5		536	5.2		1
Yes	251	4.8		322	4.0		0.86 (0.52, 1.42)

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients
** Other irrigation solutions included 10% povidone iodine (Betadine, Seton Health Care PLC, Oldham, UK), 0.2% chlorhexidine gluconate (Adam Health Care Ltd, UK), 17% ethylene-diamine-tetra-acetic acid (EDTA) (AnalaR® grade, Merck BDH, Poole, UK)

As expected, crown or root perforation created during canal location or instrumentation, significantly ($P < 0.05$) increased the hazard of tooth loss by 2-fold (HR = 2.04; 95% CI 1.33, 3.13) (Table 3.6.8). Another procedural error, fracture of instrument during canal preparation, was also found to increase tooth loss by 1.5-fold but the confidence interval was very wide. The confidence interval represents a range suggestive of 84% reduction to a 13-fold increase in tooth loss.

Although the results (Table 3.6.8, page 195) indicated that the use of higher concentration of sodium hypochlorite solution (HR = 0.88; 95% CI 0.52, 1.51) and the additional use of Betadine® (HR = 0.52; 95% CI 0.24, 1.15) or Corsodyl® (HR = 0.57; 95% CI 0.18, 1.85) for irrigation reduced tooth loss, the confidence intervals for their respective hazard ratios were all very wide. For example, the confidence interval for the hazard ratio of additional use of Corsodyl® irrigation was consistent with a range of 82% reduction to an 85% increase in tooth loss. In contrast, the additional use of EDTA solution (HR = 1.34; 95% CI 0.79, 2.27) for irrigation increased the hazard of tooth loss by 34% but the difference was not significant at the 5% level.

The presence of inter-appointment pain (HR = 1.48; 95% CI 0.80, 2.75) was associated with an increase in tooth loss but the difference was not significant at the 5% level. In contrast, the presence of inter-appointment swelling (HR = 0.92; 95% CI 0.22, 3.86) was found to have minimal effect on tooth loss (Table 3.6.8).

Extrusion of gutta-percha root filling significantly ($P < 0.05$) increased the hazard of tooth loss by 85% (HR = 1.85; 95% CI 1.10, 3.10) (Table 3.6.8). In contrast, the extrusion of sealer reduced the hazard of tooth loss by 14% (HR = 0.86; 95% CI 0.52, 1.42), again the confidence interval was very wide and consistent with a range of 48% reduction to a 42% increase in tooth loss (Table 3.6.8).

3.6.2.5 Post-operative factors

i) Post-operative restorative factors

After completion of the root canal treatment, the majority (90% for primary, 79% for secondary) of the core materials were placed at the Eastman Dental Hospital (EDH) (Table 3.6.9). The major exception was teeth requiring cast post and core for retaining the coronal restoration, which were more frequently placed by the referring dentist (Table 3.6.9).

Table 3.6.9 Number and percentage of different types of core materials placed at the EDH (otherwise by referring dentist)

		Amalgam	**Composite**	**Glass ionomer cement**	**IRM®**	**Plastic core with post**	**Cast post & core**	**Total**
1°RCT	Placed at EDH	370 (95.1%)	222 (94.9%)	52 (91.2%)	8 (66.8%)	15 (71.4%)	19 (41.3%)	**686 (90.4%)**
	Total	**389**	**234**	**57**	**12**	**21**	**46**	**759**
2°RCT	Placed at EDH	441 (90.8%)	125 (88.0%)	62 (69.7%)	12 (70.6%)	17 (36.2%)	18 (23.4%)	**675 (78.7%)**
	Total	**486**	**142**	**89**	**17**	**47**	**77**	**858**

1°RCT = primary root canal treatment; 2°RCT = secondary root canal treatment

The definitive restorations for some teeth were the plastic core materials (composite, glass ionomer cement, amalgam) placed in the access cavity (Table 3.6.10). For those teeth requiring cast restorations over the core, only a small proportion (25% for primary, 14% for secondary root canal treatment) were completed at the EDH (Table 3.6.10). A small number of teeth were still dressed with IRM® temporary cement at the follow-up appointment (Table 3.6.10).

Table 3.6.10 Number and percentage of different types of definitive restorations placed at the EDH (otherwise by referring dentist)

		Composite / Glass ionomer cement	Amalgam	Cast	IRM®	Total
1°RCT	**Placed at EDH**	247 (92.9%)	120 (96.8%)	92 (25.4%)	6 (85.7%)	**465 (61.3%)**
	Total	**266**	**124**	**362**	**7**	**759**
2°RCT	**Placed at EDH**	157 (91.8%)	123 (91.1%)	75 (13.9%)	9 (69.2%)	**364 (42.4%)**
	Total	**171**	**135**	**539**	**13**	**858**

1°RCT = primary root canal treatment; 2°RCT = secondary root canal treatment

Out of the eight possible restorative factors, 5 (type of core material, core lining, type of coronal restoration, number of proximal contacts, terminal tooth) were found to have a significant ($P < 0.05$) association with tooth loss (Table 3.6.11 - overleaf).

Teeth with glass ionomer cement (HR = 2.43; 95% CI 1.22, 4.84) or IRM® (HR = 10.08; 95% CI 4.54, 22.36) as core material were associated with a significantly ($P < 0.05$) higher hazard of tooth loss than teeth with amalgam cores (Table 3.6.11). Although those teeth with cast post and cores were also associated with more tooth loss, the difference was not significant at the 10% level. Considering the core and restoration materials were the same if the tooth was restored with a plastic filling, only the “cast post & core” was investigated further. “Core line used” was not analysed further as it was significantly associated with the core material used.

When analyzing the effect of type of restoration, all the plastic restorations (glass ionomer cement, composite, amalgam) were considered as one category. Therefore two dummy variables (cast restoration, temporary restoration) were generated (Table 3.6.11). The results revealed that teeth with cast restorations after root canal treatment were associated with 56% less tooth loss (HR = 0.44; 95% CI 0.27, 0.71) (Table 3.6.11). However, those teeth still dressed with IRM® at the follow-up appointment were associated with significantly higher hazard of tooth loss (HR = 13.60; 5.97, 31.04) (Table 3.6.11). This factor was therefore further investigated in multiple regression models.

The number of proximal contacts with adjacent teeth was initially analysed as a categorical variable (Table 3.6.11). The result revealed that the hazards of tooth loss were similar for lone standing teeth (no proximal contact) and teeth with only one adjacent tooth (one proximal contact) (HR = 1.02; 95% CI 0.35, 2.94). In contrast, teeth with both adjacent teeth present (2 proximal contacts) were associated with 51% lower hazard of extraction (HR = 0.49; 95% CI 0.18, 1.35) after treatment. The analysis was repeated by combining the data from those teeth with none or one proximal contact;

the hazard ratio for teeth with 2 proximal contacts remained similar (HR = 0.48; 95% CI 0.31, 0.96). This factor was therefore investigated further in multiple regression models.

Table 3.6.11 Effects of post-treatment restorative factors adjusted for type of treatment using Cox regression analysis

	1^oRCT		2^oRCT		
Factors	**No. of teeth**	**Loss (%)**	**No. of teeth**	**Loss (%)**	**HR adjusted for type of treatment (95% CI)**
Core material					P < 0.0001**
Amalgam	389	3.6	486	4.1	1
Composite	234	2.6	142	2.1	0.62 (0.30, 1.30)
Glass ionomer cement	57	12.3	89	7.9	2.43 (1.22, 4.84)
IRM®	12	33.3	17	29.4	10.08 (4.54, 22.36)
Post & amalgam	21	0.0	47	4.3	0.87 (0.21, 3.62)
Cast post & core	46	8.7	77	5.2	1.57 (0.72, 3.42)
Post present					
No	692	4.5	734	4.8	1
Yes	67	6.0	124	4.8	1.11 (0.51, 2.40)
Core lining used					P = 0.02**
None	353	6.8	453	6.2	1
Glass ionomer cement	83	4.8	69	1.5	0.51 (0.20, 1.27)
IRM®	323	2.2	336	3.6	0.48 (0.27, 0.86)
Type of restoration					
Cast restoration					
No	397	5.8	319	7.5	1
Yes	362	3.3	539	3.2	0.44 (0.27, 0.71)
Temporary restoration					
No	752	4.3	845	4.3	1
Yes	7	42.9	13	38.5	13.60 (5.97, 31.04)
Used as abutment					P = 0.6**
No	706	4.5	817	4.5	1
Bridge	43	4.7	35	11.4	1.61 (0.64, 4.04)
Denture	10	10.0	6	0.0	1.46 (0.22, 9.87)
No	*706*	*4.5*	*817*	*4.5*	*1*
Yes (any type)	*53*	*5.7*	*41*	*9.8*	*1.58 (0.68, 3.70)*
Number of proximal contacts					P = 0.007**
None	24	12.5	26	3.9	1
One	162	6.2	177	9.6	1.02 (0.35, 2.94)
Two	573	3.8	655	3.5	0.49 (0.18, 1.35)
Two proximal contacts					
No	186	7.0	203	8.9	1
Yes	573	3.8	655	3.5	0.48 (0.31, 0.96)
Terminal tooth					
No	643	4.0	756	4.1	1
Yes	116	7.8	102	9.8	2.07 (1.24, 3.46)

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients
** P value of test for heterogeneity for categorical factors

The effect of being the last tooth in the arch, the "terminal tooth" was also analysed. Terminal teeth were found to be associated with a significantly higher hazard of tooth loss (HR = 2.07; 95% CI 1.24, 3.46) after root canal treatment (Table 3.6.11). However, this factor was significantly (P = 0.001) correlated with the number of proximal contacts as the terminal tooth by definition can only have one or no proximal contacts. Therefore these two factors could not be entered simultaneously into a multiple regression model in the further analyses.

ii) Additional post-operative Endodontic treatment

After the initial planned treatment had been completed, some teeth required further endodontic intervention; fewer of the teeth having undergone primary root canal treatment (1.8%, 14/759) had received further endodontic treatment compared to those having undergone secondary root canal treatment (3.5%, 30/858). The difference in the proportion of teeth was statistically significant (P = 0.042). Additional treatment usually involved endodontic surgery more often than non-surgical re-treatment (Table 3.6.12).

Table 3.6.12 Frequency distribution of additional Endodontic treatment on teeth after primary and secondary root canal treatment

	No further treatment	Endodontic surgery	Non-surgical re-treatment	Total
1^{o}RCT	745 (98.2%)	13 (1.7%)	1 (0.1%)	**759 (100%)**
2^{o}RCT	828 (96.5%)	28 (3.3%)	2 (0.2%)	**858 (100%)**

The additional endodontic treatment was found to have no significant (HR = 0.92; 95% CI 0.22, 3.84) effect on tooth loss (Table 3.6.13).

Table 3.6.13 Effect of additional Endodontic treatments adjusted for the type of treatment using Cox regression analysis

	1^{o}RCT		2^{o}RCT		
Factors	**No. of teeth**	**Loss rates (%)**	**No. of teeth**	**Loss rates (%)**	**HR adjusted for type of treatment (95% CI)***
Additional treatment					
No	745	4.4	828	5.0	1
Yes	14	14.3	30	0.0	0.92 (0.22, 3.84)

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients

3.6.2.6 Summary of potential prognostic factors identified for further multiple Cox regression analyses

In summary, seventeen potential prognostic factors were identified in the single prognostic factor model with type of treatment as a covariate (Table 3.6.14). If one factor was deemed to act as a surrogate measure for another, the one with weaker effect on the hazard of tooth loss was excluded from further analyses.

Table 3.6.14 Potential prognostic factors for tooth loss after primary or secondary root canal treatment

General patient factors: 1. diabetes 2. systemic steroid therapy 3. thyroxin therapy **Pre-operative factors:** 1. pre-operative pain 2. pre-operative sinus 3. pre-operative periodontal probing depth 4. pre-operative cervical resorption 5. presence of fractured instruments 6. fate of foreign material	**Intra-operative factors:** 1. patency at canal terminus 2. blockage of any canal 3. crown or root perforation 4. extrusion of root filling into the periapical tissue **Post-operative restorative factors:** 1. cast post & core 2. type of coronal restoration 3. number of proximal contacts 4. terminal tooth

Two of the pre-operative factors (presence of fractured instruments, fate of foreign material) were unique to secondary root canal treatment. “Presence of fractured instruments” was significantly (P < 0.001) correlated with “fate of foreign material”. In addition, “fate of foreign material” was significantly (P < 0.001) correlated with “patency at apical terminus”. As both of these two factors (presence of fractured instruments and fate of foreign material) were predictive for achieving patency at canal terminus, they were not analysed further in multiple regression models.

The two factors (pre-operative perforation, intra-operative perforation) were combined into a single binary factor “presence of pre- or intra-operative perforation at mid- or coronal level” for further analyses because: (1) there were only a small number of cases with such procedural errors, and (2) perforation at a more coronal level may increase the risk of bacterial leakage or tooth fracture.

Of the post-operative restorative factors, “number of proximal contacts” and “terminal tooth” were significantly (P < 0.001) correlated as a terminal tooth could only have one proximal contact. There was, however no reason for excluding one or the other, therefore, their effects were analysed in two different models.

3.6.3 Final multiple Cox regression model building

Initially, the three medical conditions (diabetes, steroid therapy, thyroxine therapy) were entered simultaneously into a multiple Cox regression model together with type of treatment (Table 3.6.15). Both steroid therapy and thyroxine therapy did not reach the 5% significance level.

Table 3.6.15 Multiple Cox regression model incorporating type of treatment and the three medical conditions simultaneously

Factors	HR	95% CI for HR*	P value
Type of treatment			
Primary root canal treatment	1		
Secondary root canal treatment	1.10	0.69, 1.75	0.7
Diabetic			
No	1		
Yes	3.64	1.42, 9.34	0.007
Systemic steroid therapy			
No	1		
Yes	2.50	0.69, 9.10	0.2
Thyroxin therapy			
No	1		
Yes	2.20	0.79, 6.12	0.1

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients

In the next phase, type of treatment and the two medical conditions (diabetic, systemic steroid therapy) were entered simultaneously together with all the potential significant pre-operative, intra-operative and post-operative factors into a multiple Cox regression model (Appendix XI*)*. “Systemic steroid therapy” proved to have prognostic value (HR = 2.95; 95% CI 0.98, 8.83). When “thyroxin therapy” was entered into the model after dropping “systemic steroid therapy”, “thyroxin therapy” was found to have no prognostic value (HR = 1.80; 95% CI 0.57, 5.72). Thus “thyroxin therapy” was not analysed further.

"Patency at apical terminus" (HR = 0.66; 95% CI 0.26, 1.68) and "blockage of canal during treatment" (HR = 1.48; 95% CI 0.69, 3.16) failed to retain their prognostic value when they were entered into the same model. Patency at canal terminus dictates the level to which the canal could be cleaned by the instruments and chemical disinfectant. Those canals that became blocked at a later stage during canal enlargement might have been cleaned well enough with the earlier smaller instruments. Therefore it was decided to keep "patency at apical terminus" in the model but to exclude "blockage of canal" from further analyses.

Two of the post-operative restorative factors, "terminal tooth" (HR = 1.16; 95% CI 0.51, 2.65) and "two proximal contacts" (HR = 0.62; 95% CI 0.36, 1.09) were also found to have no prognostic value when they were entered into the same model. This was as expected and these two factors were analysed in separate models subsequently as there was no reason for excluding either of them.

In the final phase, the remaining 13 potential prognostic factors with exclusion of "terminal tooth" were entered simultaneously with type of treatment into model 1 (Table 3.6.16a – Overleaf). The hazard ratio of "pre-operative periodontal probing depth" had a wide confidence interval.

When "two proximal contacts" was replaced with "terminal tooth" in Model 2 (Table 3.6.16b – Overleaf), the magnitude and direction of effect of all the other prognostic factors in this model were almost the same as in model 1. It was also noted that the hazard ratios of some factors (pre-operative cervical resorption, post-operative temporary restoration) had wide confidence intervals, indicating that the corresponding estimated hazard ratios were imprecise.

There was, however, evidence that the proportional-hazards assumption had been violated (Global test: P = 0.008) for some of the prognostic factors in both models 1 and 2 (Table 3.6.17, page 203). Three factors (pre-operative pain, patency at the apical foramen, extrusion of gutta-percha root filling) have clearly violated the proportional-hazards assumptions (Table 3.6.17).

A single hazard ratio describing the effect of each of these factors is therefore inappropriate. The scaled Schoenfeld residuals over time for each of the three factors are presented in Figures 3.6.2 – 3.6.4 (Pages 203 & 204). The effect of pre-operative pain on hazard seems to stay the same until about 22 months and then declined thereafter (Figure 3.6.2); whilst the effect of patency at the apical terminus seems to increase after about 19 months post-operatively (Figure 3.6.3). Similarly, having extrusion of gutta-percha root filling did not have an effect on the hazard until about 20-22 months post-treatment; the hazard then increased thereafter (Figure 3.6.4).

Table 3.6.16 a&b Final multiple Cox regression models 1 & 2

	a) Model 1			b) Model 2		
Factors	**HR**	**95% CI for HR***	**P value**	**HR**	**95% CI for HR***	**P value**
Type of treatment						
Primary root canal treatment	1			1		
Secondary root canal treatment	1.36	0.86, 2.16	0.2	1.34	0.85, 2.12	0.2
Diabetic						
No	1			1		
Yes	3.24	1.28, 8.18	0.01	3.47	1.44, 8.41	0.006
Systemic steroid therapy						
No	1			1		
Yes	3.18	1.17, 8.72	0.02	3.59	1.31, 9.86	0.01
Pre-operative periodontal probing depth						
< 5mm	1			1		
≥ 5mm (narrow defects)	2.16	0.90, 5.14	0.08	2.48	1.06, 5.81	0.04
Pre-operative pain						
No	1			1		
Yes	2.78	1.67, 4.63	< 0.001	2.73	1.63, 4.59	< 0.001
Pre-operative sinus						
No	1			1		
Yes	2.24	1.31, 3.84	0.003	2.26	1.32, 3.86	0.003
Pre-operative cervical resorption						
No	1			1		
Yes	4.84	1.20, 19.56	0.03	4.81	1.20, 19.24	0.03
Pre- or intra-operative perforation						
No	1			1		
Yes	3.86	1.73, 8.61	0.001	3.96	1.78, 8.87	0.001
Patency at apical terminus						
No	1			1		
Yes	0.45	0.23, 0.88	0.02	0.47	0.24, 0.94	0.03
Extrusion of gutta-percha root filling						
No	1			1		
Yes	1.94	1.12, 3.36	0.02	1.87	1.08, 3.22	0.03
Cast post & core						
No	1			1		
Yes	2.59	1.14, 5.88	0.02	2.56	1.15, 5.71	0.02
Post-operative temporary restoration present						
No	1			1		
Yes	7.93	3.50, 17.96	< 0.001	8.72	3.82, 19.94	< 0.001
Post-operative cast restoration present						
No	1			1		
Yes	0.38	0.22, 0.64	< 0.001	0.42	0.25, 0.71	0.001
Two proximal contacts						
No	1			–	–	–
Yes	0.47	0.29, 0.76	0.002			
Terminal tooth						
No	–	–	–	1		
Yes				1.96	1.14, 3.38	0.016

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients

Table 3.6.17 Test of proportional hazards assumption for model 1 and model 2

	Model 1	Model 2
Factors	***P value**	***P value**
Type of treatment	0.9	0.8
Diabetic	0.9	0.9
Systemic steroid therapy	0.6	0.9
Pre-operative periodontal probing depth	0.2	0.3
Pre-operative pain	0.001	0.0005
Pre-operative sinus	0.06	0.05
Pre-operative cervical resorption	0.2	0.2
Pre- or intra-operative perforation	0.7	0.9
Patency at apical terminus	0.006	0.01
Extrusion of gutta-percha root filling	0.02	0.02
Cast post & core	0.5	0.4
Post-operative temporary restoration present	0.5	0.4
Post-operative cast restoration present	0.8	0.6
Two proximal contacts	1.0	–
Terminal tooth	–	0.4
Global test	**0.008**	**0.008**

*P value for testing for trend

Figure 3.6.2 Generalised linear regression of the scaled Schoenfeld residuals of time for "pre-operative pain"

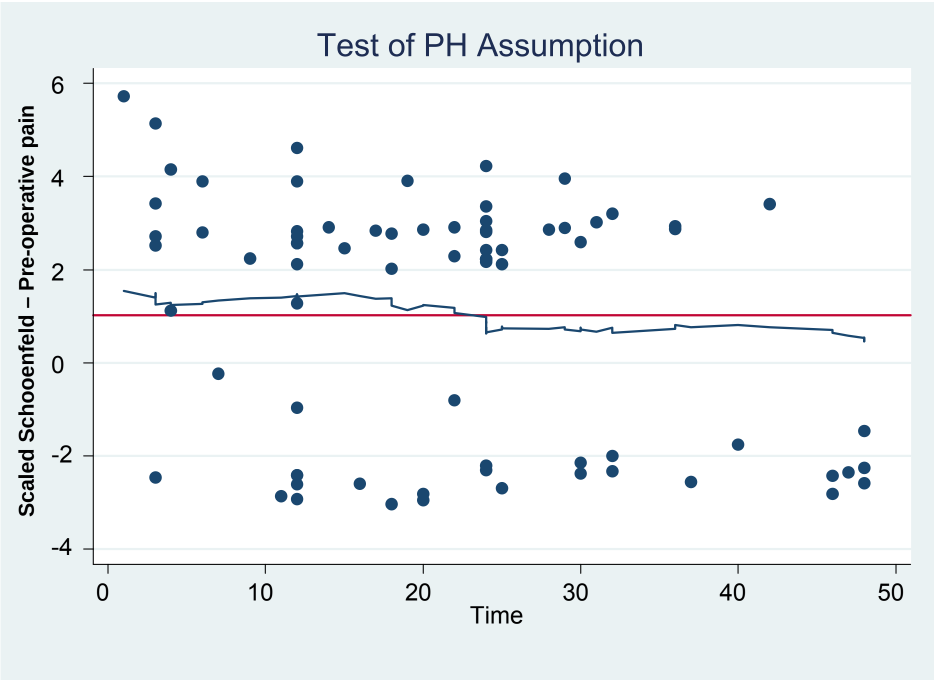


Figure 3.6.3 Generalised linear regression of the scaled Schoenfeld residuals of time for "patency at apical foramen"

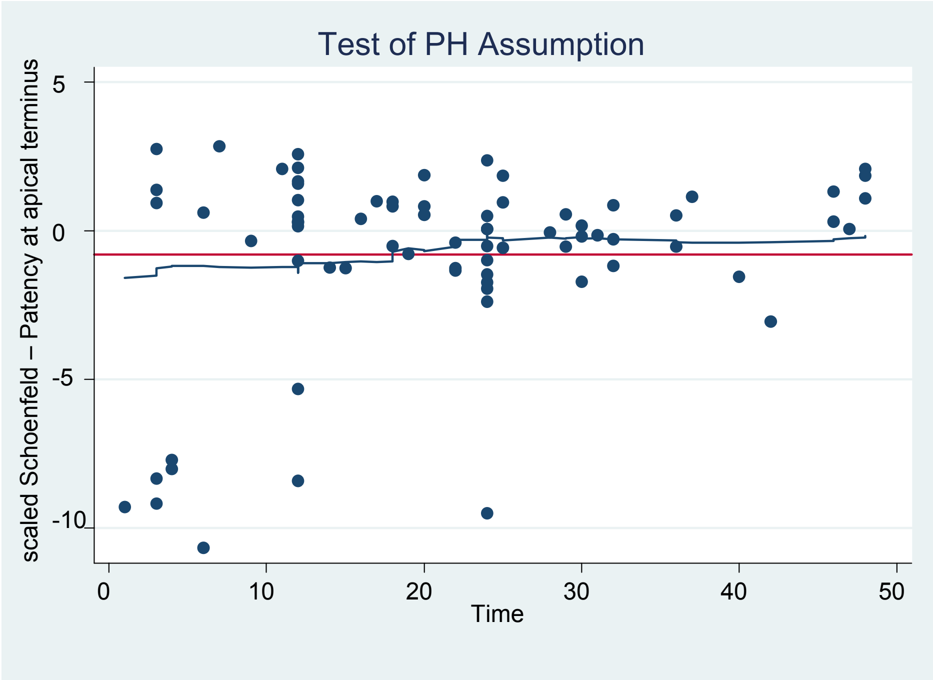
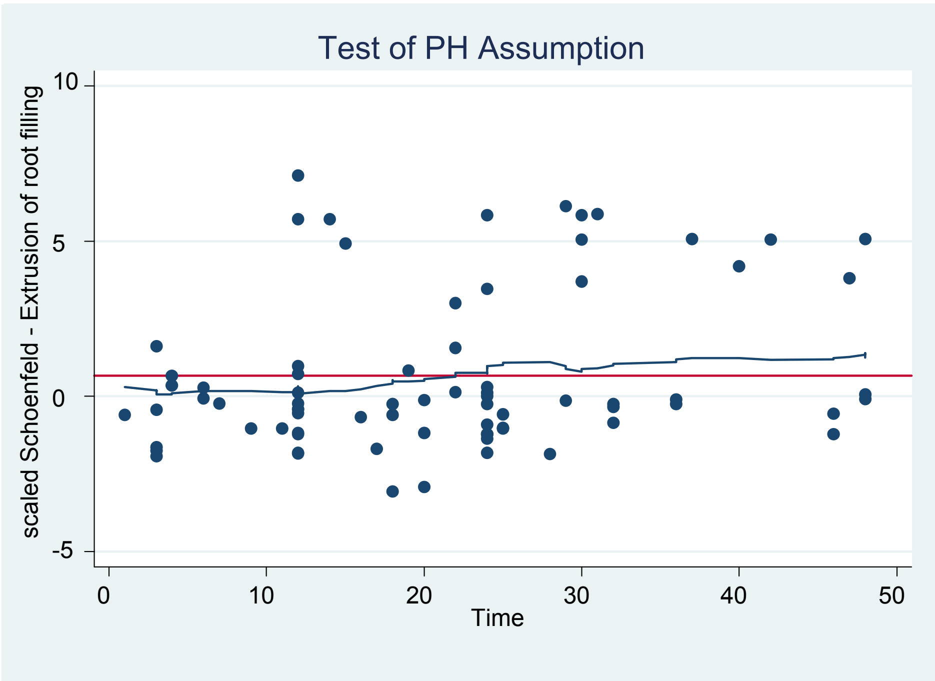


Figure 3.6.4 Generalised linear regression of the scaled Schoenfeld residuals of time for "extrusion of gutta-percha root filling"



All three prognostic factors had an effect on hazard of tooth loss that changed at about the same time after completion of treatment. The record for each observation was therefore split into two episodes at 22 months post-operatively and interaction terms between the time-band and the prognostic factors were included into the new

Cox models 1 & 2. The number of failures was about the same in the two time-bands. These models no longer violated the proportional assumptions (global test: P = 0.5 and P = 0.4 for Model 1 and Model 2, respectively). The hazard ratios and their 95% confidence intervals for most other prognostic factors were similar to those already reported in table 3.6.16a&b (Page 202). The estimated hazard ratios for “pre-operative pain”, “patency at the apical foramen” and “extrusion of gutta-percha root filling” within and beyond the 22 months post-operatively are shown in table 3.6.18a&b.

Table 3.6.18a&b Definitive models 1 & 2 presenting the effects of “pre-operative pain”, “patency at the apical foramen” and “extrusion of gutta-percha root filling” before and after 22 months post-treatment

	a) Model 1			**b) Model 2**		
Factors	**HR**	**95% CI for HR***	**P value**	**HR**	**95% CI for HR***	**P value**
Type of treatment						
Primary root canal treatment	1			1		
Secondary root canal treatment	1.33	0.85, 2.11	0.2	1.31	0.83, 2.08	0.2
Diabetic						
No	1			1		
Yes	3.21	1.27, 8.10	0.01	3.46	1.43, 8.36	0.006
Systemic steroid therapy						
No	1			1		
Yes	2.96	1.09, 8.19	0.03	3.40	1.25, 9.30	0.02
Pre-operative periodontal probing depth						
< 5mm	1			1		
≥ 5mm (narrow defects)	2.04	0.86, 4.83	0.1	2.35	1.01, 5.45	0.04
Pre-operative pain						
No	1			1		
Yes (within 22 months)	3.12	1.56, 6.25	0.001	3.10	1.53, 6.29	0.002
Yes (beyond 22 months)	2.46	1.22, 4.94	0.01	2.39	1.19, 4.82	0.02
Pre-operative sinus						
No	1			1		
Yes	2.22	1.29, 3.81	0.004	2.22	1.29, 3.82	0.004
Pre-operative cervical resorption						
No	1			1		
Yes	4.78	1.22, 18.7	0.03	4.75	1.22, 18.43	0.02
Pre- or intra-operative perforation						
No	1			1		
Yes	3.68	1.62, 8.35	0.002	3.77	1.65, 8.60	0.002
Patency at canal terminus						
No	1			1		
Yes (within 22 months)	0.29	0.13, 0.65	0.002	0.31	0.14, 0.70	0.005
Yes (beyond 22 months)	1.65	0.23, 11.88	0.6	1.65	0.22, 12.20	0.6
Extrusion of gutta-percha root filling						
No	1	1		1		
Yes (within 22 months)	1.09	0.42, 2.81	0.2	1.05	0.41, 2.72	0.9
Yes (beyond 22 months)	2.98	1.45, 6.09	0.003	2.84	1.39, 5.82	0.004
Cast post & core						
No	1			1		
Yes	2.58	1.13, 5.87	0.02	2.60	1.16, 5.74	0.02
Post-operative temporary restoration present						
No	1			1		
Yes	7.53	3.31, 17.09	< 0.001	8.26	3.58, 19.03	< 0.001
Post-operative cast restoration present						
No	1			1		
Yes	0.38	0.22, 0.64	< 0.001	0.43	0.25, 0.72	0.001
Two proximal contacts						
No	1			–	–	–
Yes	0.47	0.29, 0.76	0.002			
Terminal tooth						
No	–	–	–	1		
Yes				1.93	1.13, 3.31	0.02

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients

3.6.4 Summary of results

Of the 1617 teeth analysed, 4.7% of primary root canal treatment and 4.8% of secondary root canal treatment teeth were lost within 4 years post-operatively.

Two prognostic models, using Cox regressions, were developed to describe the effects of prognostic factors on the survival of teeth after treatment. The type of treatment did not have a significant effect on tooth survival (HR = 1.3; 95% CI 0.8, 2.1). Though, there was 30% more tooth loss after secondary root canal treatment. The respective confidence interval was, however, very wide and indicative of a range between 20% less to 110% more tooth loss following secondary root canal treatment.

In total, fourteen significant prognostic factors were identified for primary and secondary root canal treatment. Two of them were related to the patients' medical condition. Patients suffering from diabetes (HR = 3.2 – 3.4; $P \leq 0.01$) or under systemic steroid therapy (HR = 3.0–3.4 $P < 0.05$) were associated with 3 fold more tooth loss than their healthy counterparts.

Five significant pre-operative prognostic factors were identified. Pre-operative periodontal probing depths deeper than 5 mm were associated with 2-fold more tooth loss (HR = 2.0 – 2.4; P = 0.04 – 0.1). However, the confidence interval for the hazard ratio was wide representing a range between 14% reduction to 440% increase in hazard. The presence of pre-operative pain had a profound effect on tooth loss within the first 22 months after treatment (HR = 3.1; 95% CI 1.5, 6.3) with a lesser effect beyond 22 months (HR = 2.4; 95% CI 1.2, 4.9) post-operatively. The presence of a pre-operative sinus increased the hazard of tooth loss by 120% (HR = 2.2; P = 0.004) with a corresponding narrow confidence interval for the hazard ratio. The presence of pre-operative cervical root resorption was associated with almost 380% (HR = 4.8; P = 0.03) more tooth loss but the corresponding confidence interval for the hazard ratio was very wide. They indicated a range between 22% increase to 180% increase of hazard. The presence of pre- or intra-operative perforation increased tooth loss by nearly 300% (HR = 3.7; P = 0.002).

The effects of the other two intra-operative factors: patency at the apical terminus and extrusion of gutta-percha root filling material had different effects on the hazard of tooth loss before and beyond, 22 months post-operatively. Patency at the apical terminus reduced tooth loss (HR = 0.3; $P < 0.01$) within the first 22 months after treatment but had no significant effect on tooth survival beyond 22 months post-operatively. During the first 22-month period, there was upto 70% less tooth loss if patency at the apical terminus has been achieved.

Extrusion of gutta-percha root filling did not have any effect on tooth survival (HR = 1.1; 95% CI 0.4, 2.8) within the first 22 months but significantly increased the hazard of tooth loss by almost 200% beyond 22 months (HR = 3.0; 95% CI 1.5, 6.1) post-operatively.

Five significant post-operative restorative factors were identified. Teeth restored with temporary restorations were 7 – 8 times (HR = 7.5 – 8.3; $P < 0.001$) more likely to be extracted after treatment than their counterparts. On the other hand, teeth restored with a cast restoration after treatment reduced tooth loss by approximately 60% (HR = 0.4; $P < 0.001$). Teeth with restorations retained with a cast post & core were 2.6 times more likely to be extracted (HR = 2.6; P = 0.02). Teeth with two proximal contacts had 50% (HR = 0.5; P = 0.002) lower hazard of tooth loss after treatment than those teeth with none or one proximal contact. Whereas, terminal teeth were associated with almost 96% more (HR = 1.9; P = 0.02) tooth loss than those that were not located distal-most in the arch.

Chapter 4

Discussion and conclusions

4.1 Discussion of methodology

4.1.1 Systematic review and meta-analyses

4.1.1.1 Study inclusion strategy and data collection

Most of the selected studies on primary and secondary root canal treatment were prospective cohort or retrospective studies, therefore the level of evidence available is Grade B (levels 2 or 3) based on the criteria given by the Oxford centre for evidence-based medicine (Phillips *et al.* 1998). The Cochrane Oral Health group's current guidelines for a systematic review state that "The scope of the review is to include all randomised controlled trials (RCTs), where RCTs are inappropriate, rather than unavailable, other levels of evidence may be considered" (http://www.ohg.cochrane.org/forms/writing_review.pdf September 2006). By inference, therefore, "other levels of evidence" were not considered adequate for systematic review. Yet the dearth of evidence both for medicine and dentistry surely imply that there should be better guidelines for synthesis of "sub-standard" levels of evidence (Egger *et al.* 2001), whilst sufficient levels of evidence are being generated. It was decided, on review of the identified literature that the numerous observational studies, whilst not having the desired feature of randomisation or control groups, represented useful and useable data that could not be deemed inferior by any other criteria. Instead of using exclusion rules to control the heterogeneity of design, this systematic review by means of meta-analysis followed the recommendation by Stroup *et al*. (2000). Broad criteria were used for studies and the analyses were performed to investigate the effect of study characteristics on the estimated pooled success rates. Despite using such broad inclusion criteria, several "well designed" and "well executed studies" such as those by Strindberg (1956), Ørstavik *et al*. (1986, 1993), and others had to be excluded for various reasons.

The goal was to explore the available data and partition it to reveal the effect of study characteristics, general patient factors, and individual pre-, intra-, and post-operative factors on treatment outcome. A process of intuitive "triangulation" was used to compare the outcomes of different approaches of data exploration. Given the difference in the nature of root canal infection encountered during primary or secondary root canal treatment, their outcome may be influenced by different sets of prognostic factors. Therefore, meta-analyses were carried out separately on data stratified by the two treatments.

A systematic review implies an ordered, structured method for critical analysis of studies, and a coherent, simple and transparent pattern for data extraction (Mulrow 1987). Such a process would be significantly eased by a standardised format for reporting (CONSORT). Unfortunately, the studies encountered on root canal treatment revealed a very diverse pattern of presentation. In order to derive a standard system for analysis and data extraction, the reviewers first analysed the papers independently and then designed a form for data extraction. This was tested and refined until it was possible to use it without query by any of the reviewers, before finally being adopted. Ultimately, this had to involve a degree of calculation of presented data to make some of the variably presented fields more uniform, such as outcomes by tooth type or age group.

Despite this, some disagreement amongst the three reviewers (PN, KG, SR) emerged; such disagreements could be traced to a lack of clarity in the presentation of methodology and results. For some studies, data had to be extracted from the "discussion" section where it was sometimes first introduced. Most disagreements were easily resolved through discussion because the source of the discrepancy was identified and the final judgement was obvious. Only two reviewers were employed for the systematic review of secondary root canal treatment and tooth survival; as the strategy for data collection had been refined and proven, it was felt unnecessary to involve more reviewers.

4.1.1.2 Meta-analyses

An ideal clinical intervention outcome study design would include the features of randomisation and a control group. The exposure to any prognostic factors and interventions should be easily quantified and accurately recorded. Additionally, interventions should ideally be easily delivered in a discrete and standardised manner, such as in the case of a drug trial. In stark contrast, "Root canal treatment" consists of a series of interdependent steps or procedures including: tooth isolation, access, location and negotiation of root canals to their terminus, their mechanical preparation to known apical size and taper, irrigation, medication and obturation. The mechanical and chemical aspects are delivered in parallel as well as in series, and most importantly, the probability of these factors interacting in their ability to influence outcome is extremely high. It is well known that even a detailed protocol fails to allow two operators to produce the same treatment under identical conditions (Gulabivala *et al.* 2000). Given the variation in pre-operative conditions, the diversity of the cases under treatment is likely to be enormous. The study of root canal treatment outcome therefore requires that all relevant factors are recorded or accounted for in detail. In the ideal scenario, the studies should provide sufficiently detailed data to enable the exploration of the effect of these individual factors and their interactions. In theory, therefore, the estimated weighted pooled odds ratios with sub-group analyses using the method of meta-analysis should give sufficient information on the effect of individual factors and their interaction on the outcome of treatment. This view is however, countered by those who believe a perfect data set is impossible to achieve and mathematical approaches may simply average often incompatible data (Eysenck 1994). It is therefore necessary to correlate the results of meta-analyses with intuitive synthesis to derive an overview, regardless of scientific protocols.

The calculation of odds ratios requires data on the effect of a factor from the *same* studies. In most studies, outcome data were only available for one sub-category of the factor. Therefore in order not to lose the information from these studies, the present review included the estimation of *pooled success rates* (*un-weighted and weighted*) by each sub-category of a factor, which do not require paired data. Weighted pooled success rates were estimated using fixed effect and/or DeSimonian-Laird random effects weights, similar to the method used by a recent systematic review (Torabinejad *et al.* 2007).

The un-weighted pooled success rate by study characteristics of primary root canal treatment was calculated based on the approach used by Hepworth & Friedman (1997). The discrepancies and similarities in the weighted and un-weighted success rates estimated using the two approaches are well demonstrated in table 3.1.4 (Page 106). The *un-weighted* pooled success rate does not take into account, the within and between study variations, in contrast to the *weighted* pooled success rates estimated using random effects meta-analysis. The un-weighted pooled success rates were therefore not calculated for: (1) the clinical prognostic factors for primary root canal treatment; (2) study characteristics and the prognostic factors for secondary root canal treatment; and (3) study characteristics and prognostic factors for tooth survival.

The literature provides ample discussion and description of the quality of studies suitable for inclusion in meta-analyses; there is however an absence of guidelines on the *minimum number* of such studies necessary for valid meta-analyses. Some meta-analyses (Janket *et al.* 2003, Stokman *et al.* 2006) have included only two studies to provide a summary statistic for an intervention. Although this is considered acceptable by the Cochrane Oral Health group (personal communication; 2006), strictly speaking from a statistical point of view, the approach is equivalent to calculating variance on merely two observations. The relatively small number of studies included in the meta-analyses to estimate weighted pooled success rates for some factors in the present study may have produced distorted results. This problem was of more concern for the smaller number of studies available for inclusion in the review of secondary root canal treatment. The meta-analyses for several prognostic factors could be considered under-powered to demonstrate a significant influence. An alternate view is that the lack of power may have potentially over-estimated the magnitude of the effect. The reviewer therefore remains in a quandary as to the true effect! This phenomenon is not merely an isolated occurrence but potentially a widespread clinical problem, yet one that has not resulted in the abatement of a clinical service. The inference is that clinicians somehow manage to derive a working and acceptable solution. The adoption of the process of "triangulation" to locate the probable "truth" by an intuitive process of summation was acknowledged as the probable basis for this solution. It is interesting, however, that scientific literature contains scant acknowledgement of such intuitive processes as important contributors to valid decisions [Simon 1987]. The "summation" of results from quantitative (meta-analysis) and qualitative (intuitive critical appraisal) analytical approaches to draw meaningful conclusions therefore seemed sensible.

In general, the results of the meta-analyses showed substantial heterogeneity in the data. A number of study characteristics were found to be responsible for some of the heterogeneity and included; unit of assessment, criteria for success, duration after treatment, geographical origin, decade of publication and qualification of operators. In some instances, the source of statistical heterogeneity could not be identified due to the small number of studies available. These findings have significant implications in designing future studies, in which some of the above characteristics should either be standardised or accounted for during statistical analyses. The latter strategy may be more appropriate as it allows better generalisation of findings. It would also be useful to repeat the systematic review after the end of the present decade and compare the results with that obtained for previous decades.

Sensitivity tests revealed that the statistical heterogeneity could be reduced by excluding data for secondary root canal treatment from the analysis on primary root canal treatment. An example is discussed in detail in section 4.2.3.4. The difference in number of available studies of primary versus secondary root canal justified the stratification of meta-analysis for the two treatments. The issue of heterogeneity has not been addressed in previous systematic reviews on root canal treatment.

4.1.2 Prospective study

4.1.2.1 Patient/teeth cohort

The patient cohort consisted of *all* patients receiving surgical and/or non-surgical root canal treatment in the Unit of Endodontology at UCL Eastman Dental Institute/UCLH Eastman Dental Hospital. All the patients were reviewed in the same clinic, irrespective of the type of treatment. Teeth that had undergone root canal treatment but had pre-operative periodontal-endodontic lesions (n = 155) or pre-operative surgical treatment (n = 66) were not included because they contained unique factors that would complicate data analyses. The outcome of their treatment will be analysed separately beyond this thesis.

On the basis of the meta-analyses using strict criteria for treatment success, a minimum of 3 years follow-up should ideally be adopted for the present prospective study. The majority of periapical lesions had healed completely within 2 years and only 3–5% required 3 years or more for complete "radiographic healing" (Table 3.5.2, page162). This rate of healing was similar, albeit slightly faster than the previous report that 87% of all lesions healed completely, and that most "healed" lesions reduced to a size of 2mm or less within 2 years (Byström *et al.* 1987). The discrepancy may be attributed to the much smaller sample size (67 lesions) and a larger proportion of extruded root fillings (38%) in the study. Considering the potentially high drop-out rate in the follow-up of patients in London because of population mobility, cost of travel and absence from work, the duration of follow-up was reduced to a minimum of 2 years post-treatment. The potential implication of this strategy was that the success rate may be slightly under-estimated but the data from *rate of healing* revealed little impact. A two-year duration of follow-up was also adopted by another group in London (Chong *et al.* 2003) comparing the outcome of Endodontic surgery. When assessing tooth survival following root canal treatment, the cases should ideally be followed up for much longer; perhaps 10 years or more to allow estimation of the median survival rate. Such duration was not feasible within the time-frame of this thesis but the goal is to continue to follow-up all the cases, and to progressively build the sample size.

Many strategies have been adopted for improving recall rates, by which, a study may fail or succeed in reaching its goals. The problems of conducting clinical trials in mobile populations are well known and documented. The strategies include prior agreement, financial or other inducements, personal contracts, and travel or health subscription (Wang *et al.* 2004, Sponsors 2004). Although telephone calls to remind and explain the purpose of appointment were found to be very effective in encouraging attendance, it was extremely time-consuming. The strategy was later altered to limiting telephone calls to those failing to attend. The strategy adopted for inviting patients to attend for follow-up in this study proved successful with recall rates (76% for primary root canal treatment; 67% for secondary root canal treatment) much higher than the 53% median recall rates of previous studies on primary treatment but slightly lower than the 74% for secondary treatment. A much lower 2-year recall rate (47%) was achieved in a randomized controlled trial in London (Chong *et al.* 2003). It may be speculated that the 10% higher recall rate for primary compared to secondary treatment is explained by the curiosity of patients with no previous experience in root canal treatment and its outcome. During the follow-up appointment, it became apparent that patients' willingness to attend for the first follow-up was influenced by their previous rapport with the original operators and satisfaction with the treatment received. Their sense of "belonging" to a study was built-up by regular annual follow-up by the same clinician (*the author*). Other important attributes contributing to their attendance at further follow-ups were probably flexibility of recall appointment time, advice on the studied tooth as well as general restorative problems, minimum waiting time, comfortable and efficient review process, and friendly general clinical atmosphere. There were no obvious differences in age, gender or pulpal status of teeth included in or excluded from analyses. More teeth with periapical lesions, which were larger, were included in the analyses than excluded. This was as expected, as patients without tangible problems after treatment were more likely to drop out. The implication is that the reported success rate in this prospective study may be slightly under-estimated since periapical lesions and their size compromise success significantly.

The final sample sizes of 1170 roots (702 teeth) for primary and 1314 roots (750 teeth) for secondary treatment were larger than most of the previous studies using periapical healing as an outcome measure. In contrast, the sample size of 1617 teeth (759 teeth for primary treatment, 858 teeth for secondary treatment) for analyses of tooth survival, was much smaller compared to previous retrospective surveys [(Lazarski *et al.* 2001, Salehrabi & Rotstein 2004, Chen *et al.* 2007)]. The sample sizes were, however, larger than other relevant studies [(Aquiline & Caplin 2002, Caplan *et al.* 2002, Dammaschke *et al.* 2003, Alley *et al.* 2004, Lynch *et al.* 2004, Caplan *et al.* 2005, Stoll *et al.* 2005, Salvi *et al.* 2007)]. Although larger sample size improves statistical power, they may by the same token, lack detailed information or analyses.

4.1.2.2 Data collection process

One of the challenges in root canal treatment outcome research is the requirement of a system for recording complex patient and procedure characteristics. As alluded to earlier, there is potentially enormous diversity of pre-operative conditions and multiple interdependent steps during treatment. A study of root canal treatment outcome therefore requires that *all relevant* data are recorded and confounders are controlled. The problem was to balance the rigours of comprehensive data collection with compliance in accurate data acquisition. The preliminary versions of the pre-operative and intra-operative data collection forms were launched in Oct 1997. An audit by the author in 2001 showed lack of compliance in some sections of the forms, in particular in pre-operative symptoms, restorative status, and general treatment details per appointment. The forms were therefore refined taking into consideration, the results of audits, clinician feedback, and previous literature. Modified versions were introduced in 2002, and the author monitored form entries for each completed case for compliance on a regular basis. Errors or missing data were immediately corrected by returning the forms to clinicians whose motivation for completion would be that they would not be allocated further patients for their case-mix before such completion. This strategy proved excellent for compliance but was time and labour-intensive. The current system requires manual data entry onto paper forms; the labour was then duplicated during transfer to an electronic database by the author. The ultimate solution lay in computerisation and electronic format that could be populated at chair-side.

Although such a system is now in existence, the process of integrating it with a pre-existing NHS "Electronic Patient Registration" system has proved challenging.

4.1.2.3 Radiographic assessment

The intra- and inter-observer agreements were good (Kappa 0.80–0.83). The one year interval between two viewings for intra-observer agreement test was adopted. The reason for this was that the author could still remember the previously recorded outcomes 2–3 months later, which is a commonly adopted interval (Sjögren *et al.* 1990). The good agreement between the two observers may be attributed to the fact that they had previously calibrated their radiographic assessment in many different settings and studies in addition to the specific calibration for this study. The main area of disagreement lay amongst those cases with slightly widened periodontal ligament space, consistent with the findings by Reit & Hollender (1983).

It was noted that the quality of geometric reproduction of radiographic images was good without an occlusal registration record. In fact, the feasibility of using such a record was tested over 2 years (October 1999 – September 2001). During this period, an occlusal registration record was taken using silicone putty (President Putty Coltène®, Altstätten, Switzerland) on the treated tooth and its adjacent teeth immediately after completion of treatment. It was then stored in the patient's medical records after decontamination. However, in subsequent follow-up of these cases between 2000 and 2002, the repositioning of the matrix was found to be problematic. This could be traced to two factors: (1) the occlusal anatomy of many teeth had since changed as a result of new restorations placed by the referring dentist; and (2) some of the silicone records were distorted. Thus this practice was discontinued.

4.1.2.4 Statistical methods

The Generalised estimating equations (GEE) with specified "equal-correlation" between roots within teeth, used in a previous study (Hoskinson *et al.* 2002), was not adopted in the present study when analysing the prognostic factors for periapical healing. Given that "patients" are considered at the highest level in the hierarchical data structure, the clustering of roots within patients rather than within teeth were accounted for in the logistic regression analysis. The "equal-correlation structure" for roots within patients may be miss-specified as in reality their correlation may vary from patient to patient. Thus the present investigation did not specify any within- and between-patient correlation structure for roots but only adjusted for the clustering within patients when estimating the confidence intervals for odds ratios. Random effects multi-level models could be used to account for all three levels and in particular to estimate the variability of the patients' contribution to the periapical healing. The estimation methods for binary outcomes are, however, not always straightforward when the number of level 1 units (roots) within level 2 (teeth) and level 3 (patients) is small (Goldstein 2003).

Similarly, the present investigation on tooth survival also adjusted for clustering of teeth across patients in the Cox proportional hazards regression models with robust standard errors accounting for the number of clusters and units. The hierarchical data structure has not been addressed in previous studies on tooth survival. The zero time point for the survival analysis could have been chosen in different ways: (1) time of diagnosis of pulpal/periapical disease; (2) commencement of root canal treatment; or (3) completion of root canal treatment. The first date was unknown as pulpal/periapical disease of the teeth was initially diagnosed by the referring dentist. Although the date of commencement of treatment could be extracted from the data collection form, the time interval between commencement and completion of treatment varied substantially for many reasons. Given the objective of the present study, to investigate tooth survival upto 4 years after treatment, the date of treatment completion was selected as the entry time in order to have a clear-cut end point for the study.

4.2 Discussion of results

4.2.1 General results for meta-analyses

The literature search for meta-analyses on periapical healing found a larger number of studies on primary (n = 119 upto end of 2003) than on secondary (n = 40 upto end of 2006) root canal treatment. It was also noted that half of the articles on secondary treatment were published in the 1990’s and 2000’s, whilst those on primary treatment were more evenly distributed amongst the different decades since 1960. This difference may reflect the general global increase in awareness of dental health, tooth preservation and expansion in availability of aids and techniques to facilitate non-surgical root canal re-treatment [(Carr 1992)]. Consistent with this observation, from 1992 to 2002, the number of *surgical* re-treatments carried out within the National Health Service in UK had reduced by one third and this figure has continued to decline in recent years [(Dental Practice Board 2005)].

In comparison, only 31 studies on tooth survival after primary root canal treatment had been published upto the end of 2007 whilst none has specifically investigated tooth survival after secondary treatment. Most aimed to investigate the survival of the restoration rather then the root-treated tooth. Survival of root-treated teeth only began to attract the attention of Endodontic researchers when the survival of the discipline was perceived to be challenged by the putative predictability of the alternative treatment of implant-retained single unit restorations [(Naert *et al.* 2002)], since the mid-2000’s.

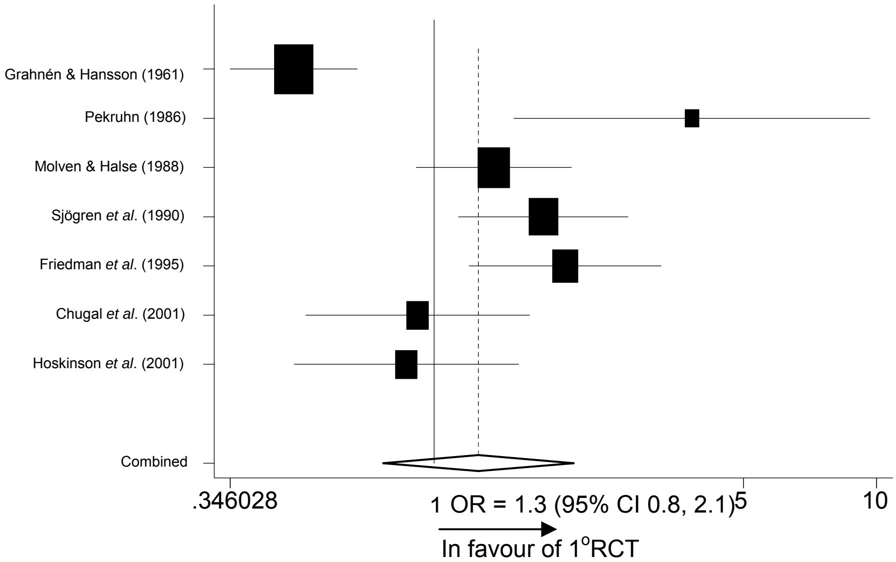
4.2.2 Success rates for primary and secondary root canal treatment based on different outcome measures

From the meta-analysis of primary root canal treatment data on periapical healing, the significant difference (10%) in success rates judged by strict (75%) or loose (85%) radiographic criteria was as expected. The negligible difference in the weighted pooled success rates by strict 76.7% and loose 77.2% criteria for secondary treatment was surprising. The discrepancy could be attributed to the substantially smaller number of studies on secondary treatment contributing to the outcome data on loose (n = 8) compared to strict (n = 14) criteria, together with a possible outlier (Danin *et al.* 1996) in the pool (Figure 3.2.5). Exclusion of this study, increased the pooled success rate for loose criteria by 7%, even though it was still slightly lower than that for primary treatment.

There were greater variations in the success of primary root canal treatment by each factor based on loose rather than strict criteria. It is likely that this is due to greater subjectivity in judging partial healing of a lesion than complete healing. This speculation could be supported by the inter-observer agreement on assessing radiographic outcome for the prospective study. Most disagreements occurred on cases judged as incomplete healing.

The slightly higher weighted pooled success rate based on strict criteria for secondary (77%, 14 studies) compared to primary (74%, 40 studies) root canal treatment, was unexpected. This finding contradicts the commonly held belief (Selden *et al.* 1974, Pekruhn 1986, Sjögren *et al.* 1990, Friedman *et al.* 1995) that primary root canal treatment is associated with better outcome than secondary treatment due to the difference in the nature (Gulabivala 2004) and location of root canal infection (Nair *et al.* 2005). Eight of the studies had presented stratified outcome data for primary *and* secondary treatment, of which seven had presented data based on strict criteria. It was noted that the relative proportion of roots/teeth with secondary treatment was low (4% to 51%). Although comparison of the outcome of the two treatments using meta-analysis was not one of the original aims of this thesis, it *was* carried out using published data in order to allow comparison with the results from the present prospective study (Figure 4.2.1 – Overleaf). It shows that primary treatment was associated with higher odds of success (OR = 1.26; 95% CI: 0.77, 2.07) but the difference was not significant (P = 0.4) (Figure 4.2.1). The results of the present prospective study found a very similar odds ratio (OR = 1.28; 95% CI: 0.91, 1.82) when comparing the success rates of primary and secondary treatments. Based on the odds ratios estimated, it may be concluded that the complete periapical healing after primary treatment is slightly more prevalent than after secondary treatment.

Figure 4.2.1 Comparison of the odds of success of primary (1^{o}RCT) and secondary root canal treatment based on data from previous studies



The meta-analyses of data based on strict criteria for healing after primary and secondary root canal treatment gave success rates at 4 years of 84% and 83%, respectively. These were similar to 83% and 80%, respectively reported in the present prospective study.

Meta-analyses revealed that the overall success rates for primary and secondary root canal treatment were not affected by “year of publication” or “geographic location of study”. In the former factor, the measure of true interest should really be the “year in which treatment was carried out” but few studies provided this information. Nevertheless, the absence of obvious improvement in success rates by the year of publication suggests that the advances in technology and materials used for root canal treatment do not appear to have influenced treatment outcome significantly. Such a suggestion is strongly refuted by endodontists on the grounds that the apparent lack of improvement in success rates is a function of more adventurous case selection fuelled by confidence in better skills and outcomes. The validity of this proposition is discussed later. For the present, it is argued that lack of improvement in success rates could be attributed to the fact that, whilst technology has improved instruments and materials to achieve a set of goals, the principles underpinning those goals have not changed over the duration covered by this review [(Hall 1928)]. The suggestion is that the concepts underpinning the treatment need to be overhauled rather than merely making the accepted steps more efficient. This brings to the fore, the classic debate about the relative value of biologic versus the technical principles in dentistry [(Noyes 1922, Naidorf 1972)]. Noyes (1922) lamented that dentists were not trained to think in biologic concepts but to act in mechanical procedures; whilst Naidorf (1972) applauding the technical excellence achieved by the pre-occupation of dentists with this element, deplored the lack of biologic awareness of the basic pathology of the problem or the biologic consequences of the treatment. Modern clinical academics in this discipline would probably sustain the validity of these assertions, even today. It is interesting to note that the success rates of studies from the North American countries, where the use of contemporary technology is probably most widely recommended and adopted, fared no better than those from other countries. Furthermore, the adoption of strict radiographic criteria and microbiological awareness in their approach appeared to bring better outcomes in studies performed in the Scandinavian countries. This speculation is important because it centres around the debates that raged in the 1960's and 1970's about the value of the microbial culture test in informing the progress of treatment, a practice, long since abandoned as unnecessary (Engström *et al.* 1964, Mikkelsen & Theilade 1969, Oliet & Sorin 1969, Morse 1971, Sims 1973, Frank *et al.* 1978, Molander *et al.* 1996a&b). This ultimately led to the adoption of single-visit treatment by many endodontists on the basis of the cost-benefit analysis (Spångberg 2001), an issue discussed further later. The historical importance of this biological versus technical debate is important to appreciate, because it fundamentally changed the way root canal treatment was conceived and practiced; from a microbially-aware post-focal infection era, to one dominated by a technological awareness but relative microbiological ignorance.

The problem of geographic location also merits closer inspection, as sometimes, a single study may report pooled data from multi-centre evaluations (Friedman *et al.* 1995). It is known that there are geographic variations in the teaching and practice of root canal treatment based on local cultural beliefs and economic conditions (Qualtrough & Dummer 1997, Qualtrough *et al.* 1999, McColl *et al.* 1999, Tsuneishi *et al.* 2005, Touré *et al.* 2008). Given, this wide spectrum of variation in adoption of root canal treatment protocols, it is indeed surprising that geographic location of study did not influence the outcome, it may perhaps be argued that despite variation in teachings and practice, in each country, the protocols adopted in the academic institutes, where the majority of studies had been conducted, could have been relatively uniform.

Meta-analysis of published data on tooth survival revealed a 93% (95% CI: 92%, 94%) 4–5 year survival rate; this was similar to the 95% (95% CI: 94%, 97%) tooth survival rate for primary or secondary treatment in the present prospective study. The 8–10 year survival rate (86.7% [95% CI 81.6%, 91.8%]) estimated from meta-analysis was 7–8% lower, suggesting that tooth loss continued many years after treatment and warrants a much longer duration of follow-up in future studies. The range of survival rates from the present meta-analyses and prospective study was consistent with the previous meta-analyses on tooth survival after root canal treatment (Torabinejad *et al.* 2007). The tooth survival rate from the present prospective study was comparable with the previous estimated pooled weighted 2–4 year survival rates for implant-supported single crowns (96% [95% CI: 94%, 97%]); but much higher than the respective figures for tooth extraction with fixed-prosthesis replacement (78%–79%) (Torabinejad *et al.* 2007).

These results may infer that both the options of root canal re-treatment and replacement with an implant-supported single crown should be considered as alternatives during treatment planning for teeth with endodontic problems.

4.2.3 Prognostic factors for success of treatment using absence of clinical and radiographic signs of periapical disease as outcome measure

The following discussions on the effect of prognostic factors are based on all the analytical approaches adopted in this thesis: (1) intuitive synthesis of the findings from individual studies; (2) comparison of the pooled weighted success rates by each factor based on previous data; (3) calculation of the pooled odds ratio for each factor based on previous data; and (4) calculation of the odds ratio for each factor based on the data from the present prospective study.

4.2.3.1 General patient factors

In the assessment of patients' gender and age, the results of all the above analytical approaches were available and all concurred in their findings. The results confirmed that there was no obvious difference in success rate between male and female patients, consistent with the fact that there is no known difference in healing potential between genders. Given that presence or absence of pain was a criterion in the judgement of treatment outcome in a number of previous and the present prospective studies, the documented difference in pain perception between genders, which has been ascribed to hormonal differences, may potentially have had an important bearing on this discussion (Macfarlane *et al.* 2002). In a previous study (Polycarpou *et al.* 2002), female patients were found to have significantly higher (OR = 4.59; 95% CI 1.13–18.65) odds of suffering from chronic post-treatment pain than male patients. Closer inspection of the present data revealed the same trend but the magnitude of difference was much lower (OR = 1.9; 95% CI 0.9, 4.3), explaining the lack of influence on the overall outcome of treatment in the present study. The larger effect of gender on pain experience reported by Polycarpou *et al*. (2002) may be attributed to their much smaller sample size (103 teeth) and adoption of a minimal of 1-year rather than 2-year follow-up. The small sample size may result in over but imprecise estimation of the effect which is demonstrated by the very wide confidence interval for the odds ratio. The shorter duration after treatment may include some cases with the lesions that have just "healed completely" by 1 year but were still accompanied by discomfort/mild pain. During the consecutive annual follow-up of the current cohort, the subjective impression was that in many instances, such residual pain/discomfort spontaneously resolved in the subsequent follow-ups. This observation therefore prompted the initiation of a separate study to monitor the clinical course of pain/discomfort during the initial periapical healing. The outcome of this study would be useful for decision-making in adopting a "monitoring" or "interventionist" approach to management.

A trend of pooled success rates decreasing with increase in age was noted from the meta-analysis of primary root canal treatment data, although there was no evidence of significant difference in pooled success rates by the age bands. This observation is consistent with the hypothesis that older patients may have poorer healing ability due to aging (Mogford *et al*. 2004), malnutrition (Chernoff 2004) or systemic diseases that are more prevalent in old age, such as diabetes (Cowie *et al*. 2006, Forouhi *et al*. 2006). Such a trend in success rate by age (OR = 1) was not observed in the present prospective study for either primary or secondary treatment. The discrepancy between findings from meta-analysis and prospective study could be attributable to the fact that age was analysed as a continuous rather than categorical variable in the latter.

Previous evidence for the influence of medical health on treatment outcome is weak with reporting of contradictory results (Storms 1969, Fouad & Burleson 2003, Marending *et al*. 2005, Quesnell *et al*. 2005, Shetty *et al*. 2006, Suchina *et al*. 2006, Doyles *et al*. 2007). The investigation of the influence of medical health on treatment outcome in the present prospective study was compromised by the small proportion of patients suffering from systemic diseases. Out of the many medical conditions reported by patients, only those that were more prevalent were selected for statistical analyses. Less than 10% of the cases exhibited medical conditions, explaining the spuriously large discrepancy in their effects on primary and secondary treatment found in the univariable regression analyses. The present patient cohort may not be a true representation of the London/England population. For example, the prevalence of diabetes for all persons in England was 4% in 2001, whereas only 2% of the studied patients reported suffering from diabetes. Many of the patients with severe medical problems may have been referred to Special Needs Clinics in Community Dental Centres. For appropriate investigation of the effect of medical conditions, a prospective follow-up of two matching cohorts with the only difference being the medical condition under investigation is the preferable study design. None of the previous studies had adopted such a design; identification of matching controls would be the main challenge in such a study.

It was the subjective observation of the author that the rate and pattern of periapical healing were similar amongst teeth within the same patient but varied substantially between patients. Age may also be an important factor affecting the *rate* of healing. It was noticed that periapical lesions in teenagers seemed to heal completely within one year. On the basis of these subjective observations, previous reports on the impact of PMN function and quantity on the size of periapical lesion (Kawashima *et al*. 1999, Majorana *et al*. 1999, Stashenko *et al*. 1995), and the previous findings on the impact of specific medical conditions on treatment outcome, further comprehensive investigations on the effects of host responses on treatment outcomes are required. Since ongoing treatment for the medical condition may also influence the findings, perhaps appropriate genetic or biochemical markers rather than individual medical conditions would be more preferable as potential prognostic factors (de Sá et al. 2007, Kann 2007).

4.2.3.2 Tooth and root morphological type

There is a widespread perception amongst dentists that the simpler anatomy of single rooted teeth makes their management more amenable and expect their outcomes to be higher and predictable. Such anticipation has driven the thinking behind teaching at many dental schools in the past and even currently. The outcomes of studies such as this still surprise many; tooth type was not found to confer any significant influence on outcome. This was confirmed by the meta-analyses, prospective study, and individual studies. Despite this, from a training perspective, the commencement of teaching of the root canal treatment procedure on single-rooted teeth has merit. The reason is that such teeth are indeed technically less demanding and would be useful training ground at a time when the operator's technical skills are still under development. If indeed, the technical skills of the operator play a part in the satisfactory completion of the procedure and then in turn, the periapical healing, then stratification of data on tooth type by operator skill should reveal a difference in success rates between single-rooted and multi-rooted teeth amongst inexperienced operators but not amongst experienced operators. There was insufficient data to test this hypothesis. The importance of controlling the pre-operative status of teeth was confirmed in the present prospective analysis. In the univariable analyses, tooth/root type were found to have a significant association with success rate but this effect reduced (albeit with very wide confidence intervals) once the analyses were adjusted for presence and size of pre-operative periapical lesion. The results appear to infer that the complex canal anatomy associated with molar teeth does not negatively influence the outcome of root canal treatment. Perhaps more important is the issue of apical anatomy and its infection (Wada *et al*. 1998, Nair *et al*. 2005) which may vary less between tooth types (Vertucci 1984).

Given the absence of obvious improvement in success rates by "year of publication" in the meta-analysis, the offered explanation that the "apparent" lack of improvement in success rates was a function of more adventurous case selection in recent years, may be rebutted on the grounds that tooth type, age, gender and patient's health did not significantly influence outcomes of primary or secondary root canal treatment. Considering that meta-regression analysis revealed that "qualification of operator" made no contribution to the statistical heterogeneity in the estimated combined effects of these three factors, the results of the meta-analyses and present prospective study suggest that there are hitherto unmeasured factors that inform the designation of case complexity for referral. Perhaps the criteria for endodontic case complexity should be reviewed and modified (http://www.aae.org/NR/rdonlyres/A5180AAE-

02C2-45AB-8D46-81B033B31038/0/2006CaseDifficultyAssessmentForm.pdf, http://www.rcseng.ac.uk/fds/docs/complexityassessment.pdf).

4.2.3.3 Pre-operative conditions of teeth

Many pre-operative conditions of the teeth have an impact on treatment outcome: pulpal vitality status; periapical status; size of periapical lesion; history of trauma; presence of resorption; fracture; cracks; swelling; and sinus. Only three factors (pre-operative vitality of teeth, periapical status and size of periapical lesion) were found to be well recorded and researched in previous studies. Root canal treatment is an intervention used to manage two distinct biological entities; at the one extreme, the diseased but vital pulp with an absence of periapical disease and at the other extreme, the necrotic, infected pulp/space with an established periapical lesion. In reality, though, the clinician faces a continuous spectrum of pulpal/periapical conditions that can be difficult to diagnose accurately because of limitations in the sensitivity and specificity of available methods (Dummer *et al.* 1980, Hyman & Cohen 1984). The pulpal status in the present prospective study was initially determined using thermal and electric pulp tests and confirmed after accessing the root canal during treatment. This issue has not been addressed in most previous studies. The diversity of presenting pulpal/periapical conditions was demonstrated in the present prospective study: 21% of the roots with vital pulp tissue were associated with slightly widened periodontal ligament space apically and 14% even had a periapical lesion. Moreover, a periapical lesion was not present in 24% of the roots with non-vital pulps. The importance of this lies in the fact that the pulpal and more importantly the periapical conditions have a profound effect on the treatment outcome.

The vitality of pulp was reported as a significant influencing factor by only four of the 14 selected previous studies that had analysed this factor statistically. The present meta-analysis of data pooled from 18 studies, however, revealed that teeth with vital pulps had significantly higher success rates (5%–9% or OR = 1.8 [1.4, 2.3]) than non-vital teeth, consistent with the results of a previous meta-analysis by Kojima *et al*. (2004). This demonstrates the value of meta-analyses in increasing statistical power by pooling data from individual studies. The effect of the interplay between pulp non-vitality and periapical disease on treatment outcome is demonstrated by the following observations from the meta-analysis. Elimination of data on "non-vital teeth with periapical lesions" reduced the difference in success rates between "vital" and "non-vital teeth" to a negligible level (< 0.5% or the odds ratio to 1.1 [0.7, 1.7]). In contrast, elimination of the data on "non-vital teeth without periapical lesions" increased the difference in success rates between "vital" and "non-vital teeth" to 10% or the odds ratio to 2.4 (1.8, 3.1). The important influence of the periapical status was further confirmed by the significant difference (9%–13%, OR = 2.0 [1.4, 2.8]) in success rates between non-vital teeth with and without periapical lesion. The above findings from the meta-analyses were again corroborated by the results of the present prospective study, which revealed the crude odds ratio for pulpal status to be 2.4 (1.5, 3.7). This reduced to 1.8 (1.1, 2.9) after adjusting for presence of periapical lesion and further to 1.6 (1.0, 2.7) (*results not shown*) after adjusting for both presence and size of periapical lesion. The odds ratio for absence and presence of periapical lesion was 1.96 (95% CI 1.25, 3.13) in the present prospective study, similar to the estimate (OR = 1.95 [95% CI 1.35, 2.81]) from the meta-analysis. The explanation for these clinical observations lies in the knowledge that non-vitality is not always associated with root canal infection (Bergenholtz 1974), whilst the presence of a periapical lesion always signifies the presence of root canal infection (Sundqvist 1976). The degree of correlation is compromised by the relative lack of sensitivity of conventional two-dimensional radiographs in detecting periapical lesions. Four percent of the cases in the prospective study presented with no detectable periapical radiolucent lesion but were associated with pain, sinus or swelling at follow-up. Without the facility of cone beam volumetric tomography, those cases with persistent pain but absence of periapical lesion were further investigated using cross-sectional tomography (ScanOra®, Orion Co, Espoo, Finland). The diagnostic value of this instrument was compromised by the fact that the focal trough was too imprecise to localise the image exactly and solely at the root apex. The quality of image was further compromised when taken at an oblique angle to the site of interest (Peltola & Mattila 2004).

The size of periapical lesion has been shown to influence the decision to intervene by both patients and clinicians (Reit & Gröndahl 1984). The meta-analyses revealed no significant difference in success rates between teeth with small (< 5 mm) or large (≥ 5 mm) lesions undergoing primary root canal treatment but the difference was significant for secondary treatment. Some of the heterogeneity of the data could be explained by "unit of outcome assessment" and "duration after treatment". On the basis of meta-analyses findings and the lack of influence reported by studies (Strindberg 1956, Byström *et al*. 1987, Sjögren *et al*. 1990, Sjögren *et al*. 1997) that have followed-up the cases for longer duration, it may be concluded that there is no difference in treatment outcome with large or small periapical lesions, only that the former require longer to heal completely. This neat explanation was however, not supported by the findings from the present prospective study. The size of periapical lesion was analysed as a continuous variable and was found to have a significant influence (OR = 0.86; 95% CI: 0.81, 0.91) on the success of both primary and secondary treatment even after adjusting the results by presence of periapical lesion and duration after treatment. This was in agreement with two previous studies (Chugal *et al*. 2001, Hoskinson *et al*. 2002), which also analysed this factor as a continuous variable. This discrepancy highlights the problems in dichotomisation of a continuous variable (Royston *et al*. 2006) as discussed in *section 1.9.2.1*. The lack of influence by duration after treatment (OR = 1.01; 95% CI: 1.00, 1.02) was unexpected but evidently irrefutable owing to the fact that 91%–95% of complete healing of periapical lesions took place within 2 years after treatment. The discrepancy between the results of meta-analysis and the present prospective study could be attributed to the dichotomization of size of lesion for meta-analysis. The negative influence by size of lesion also has a ready biological explanation; microbiological findings have confirmed that the diversity of bacteria (by number of species and their relative richness) increased in root canals associated with larger periapical lesions [(Sundqvist 1976)]. The infection was more likely to persist in those canals with a higher number of bacteria pre-operatively [(Byström & Sundqvist 1981)]. Larger lesions may represent longer-standing root canal infections that may have penetrated deeper into dentinal tubules and accessory anatomies in the complex canal system [(Shovelton 1964)] where mechanical and chemical decontamination procedures could not easily reach. Larger lesions may also represent cystic formation or extra-radicular infection rendering non-surgical root canal treatment ineffective [(Nair 2006)]. Finally, the host response may also play a part, as patients with larger lesions may respond less favourably to residual bacteria, the presence of which are inevitable following current treatment protocols [(Nair *et al.* 2005)]. All of the above are purely speculation and may crystallise into distinct questions for further biological research into the nature of interaction between host, bacterial infection and treatment intervention. In future, Cone-beam CT may be used to determine the size of a lesion.

Most of the other pre-operative factors investigated (pain, tooth tenderness to percussion, soft tissue tenderness to palpation, soft tissue swelling, soft tissue sinus, periodontal probing defect of endodontic origin, root resorption) were simply different clinical manifestations of the same periapical disease. They may therefore act as surrogate measures or complement the presence and size of periapical lesion in measuring various phases or severity of periapical diseases within a broad continuous spectrum. Of these, only "presence of sinus" was found to be a significant prognostic factor even after adjusting for presence and size of lesion and other prognostic factors. This finding was in contrast to that by Chugal *et al*. (2001) who reported that presence of sinus did not add any prognostic value to that provided by presence and size of lesion. The discrepancy may be attributed to the much smaller sample size (200 teeth, 441 roots) in their study. The negative impact of sinus tract on periapical healing could not be readily explained by the type and quantity of the implicated intra-radicular bacteria (*P. endodontalis, L. buccalis, P. gingivalis, F. nucleatum*) [(Sassone *et al*. 2008b)] as they have not been reported as resistant to current root canal decontamination procedures. On the other hand, refractory cases presenting with persistent sinus tracts have been reported to be associated with extra-radicular infection with actinomyces [(Happonen *et al*. 1986)] or coccal- and fungal-form micro-organsims [(Ferreira *et al*. 2004)]. A sinus tract may facilitate an alternative nutrient supply to maintain both extra-radicular periapical infection as well as apical residual bacteria, possibly explaining its negative influence on the success of treatment, independent of the presence and size of periapical lesion.

Although pre-operative swelling was excluded during the building of the final logistic regression model, this factor was found to have prognostic value even when its effect was adjusted for presence and size of periapical lesion. It may therefore be reasonable to speculate that its presence indeed has significant "clinical" prognostic value. Similar to "presence of sinus", the effect of "presence of swelling" could not readily be explained by the intra-radicular bacteria implicated for this condition as they are mostly Gram-negative anaerobes (Sundqvist 1976, Gomes *et al.* 1994, 1996, 2004) which have not been reported as resistant to NaOCl irrigant or $Ca(OH)_2$ medicament. Perhaps, the bacteria associated with swelling are strain rather then species dependent. Pre-operative swelling due to abscess or cellulitis, may represent a weak host response (Slots & Thomas 1992) to bacterial irritation; this weak immune response to the post-treatment residual infection may therefore potentially lead to treatment failure. On the other hand, it may also represent an exaggerated host response to bacterial irritation; similarly any post-treatment residual infection could also elicit an exaggerated response, leading to treatment failure (Seltzer & Naidorf 1985).

The very small and insignificant influence of the pre-operative symptoms on periapical healing may be explained by the fact that the symptoms recorded had not been stratified for pulpal or periapical origin. Symptoms of pulpal origin are not expected to have any effect on periapical healing as by inference the pulp would still be vital at the time of treatment. Whereas, symptoms of periapical origin should have the same effect as "presence of periapical lesion" since they indicate probable acute exacerbation with the bacterial front extending into the lesion (Nair 1987). The observations and findings on pre-operative signs and symptoms indicate that the bacterial/host interaction has a significant role in periapical healing. Thus, further investigation into this interaction is crucial for better insight into the rationale for root canal treatment and to better inform customised treatment for individuals with specific problems.

Pre-operative factors unique to secondary root canal treatment (time interval between primary and secondary treatments, quality of pre-existing root filling, pre-existing canal content, root perforation, root canal obstruction) were poorly investigated in previous studies. The effects of all these factors except "time interval between primary and secondary treatment" were investigated in the present prospective study. The effect of this factor could not be analysed because it was not possible to obtain the precise point in time when the previous primary treatment had commenced/completed. In many of the secondary treatment cases, the referring dentist was different from that providing the primary treatment. Nevertheless, none of these factors were found to have a direct influence on the success of secondary root canal treatment. The present study found that the success rates for roots with satisfactory pre-existing root fillings (absence of voids and extended to 2 mm within radiographic apex) were 6% lower than those with unsatisfactory pre-existing root fillings, but the difference was not significant after adjusting the results for periapical lesion. Although following the same trend, this finding was in contrast to the Toronto study (Farzaneh *et al*. 2004b, de Chevigny *et al*. 2008b) where the success rate for teeth with satisfactory pre-existing root filling was significantly lower (19%–22%). The discrepancy could be attributed to the fact that the latter study used tooth as a unit of outcome assessment, only included teeth with periapical lesions in the analysis, and had a much smaller sample size (n = 99–211 teeth). Two explanations were advanced for the observation by the authors of the Toronto study (Farzaneh *et al*. 2004b, de Chevigny *et al*. 2008b): (1) in teeth with adequate pre-operative root filling, the persisting infection may have been less susceptible to routine secondary treatment procedures; (2) the persistent lesion may have been caused by extra-radicular infection, a true cyst or foreign body reaction unresponsive to secondary treatment. In contrast, those canals with under-extended pre-existing root fillings may be due to natural or iatrogenic blockages that could not be re-negotiated to the apical terminus during secondary treatment and therefore compromised outcome. In agreement with the latter argument, the present study also found that short root fillings (>2 mm short of canal terminus) were more frequently (5%) present in roots with unsatisfactory pre-operative root fillings than in roots with satisfactory pre-operative root fillings (*results not shown*).

The type and fate of pre-operative foreign materials/separated instruments were all found to have a significant influence on secondary treatment outcome in univariable regression analyses. Clinically, the type of foreign material/fractured instrument, fate of foreign material and finally, ability to achieve patency at the canal terminus were in the same confounding pathway. Although the fate of foreign material proved to have prognostic value even after adjustment for presence and size of periapical lesion, this factor was removed from further analysis because “patency at canal terminus” had a more direct influence on treatment outcome from a clinical perspective. The results may infer that as long as patency could be achieved at the canal terminus, success of secondary treatment would not be affected by type of foreign material whether it was removed or bypassed. Only half the fractured instruments were successfully removed or bypassed, explaining their association with lower success rates. The present finding was consistent with the 49–53% of fractured instrument removal rate by postgraduate students in Athens, Greece (Tzanetakis *et al*. 2008) or dentists in Wuhan, China (Shen *et al*. 2004). Higher rates of instrument removal (87%) (Suter *et al*. 2005) and success rates (91%) (Gorni & Gagliani 2004) have been reported by experienced specialists. The lower fractured instrument removal rate at the Eastman may in addition be explained by the adopted principle of preservation of root dentine to facilitate tooth survival (Sathorn *et al*. 2005a) rather than sacrificing dentine at any cost for instrument removal.

Procedural errors may involve instrument fracture or uncontrolled dentine damage, which lead to perforation or canal obstruction, both of which were investigated in the present study. Due to the small proportion of cases with pre-operative or intra-operative perforation, their data were pooled in order to improve statistical power. The presence of perforation at the coronal or mid-root level may increase bacterial contamination during and after treatment and was found to significantly reduce the odds of success by 70%. This was consistent with the findings from the present meta-analysis and the Toronto study (Farzaneh *et al*. 2004b, de Chevigny *et al*. 2008b). Previous data had indicated that the use of MTA™ as perforation repair material may improve the success of treatment of these cases (Main *et al*. 2004, de Chevigny *et al*. 2008b). The present prospective data however, did not favour any repair material as being superior. As already highlighted by Sjögren *et al*. (1990), it was not possible in the present study to distinguish whether the pre-operative canal blockage was caused by natural calcification or iatrogenic errors. Therefore its influence on success of treatment will be discussed together with the intra-operative factors: "patency at canal terminus" and "apical extent of canal preparation", in the following sections.

4.2.3.4 Intra-operative factors

In contrast to the pre-operative data, previous investigations on intra-operative factors were comparatively deficient (Table 3.1.3 [page 105] & 3.2.4 [page 136]); pooled success rates rather than pooled estimates of odds ratios could be calculated for most factors using meta-analysis. Even when the pooled success rates were estimated, the synthesis was compromised by the small number of studies available. Definitive conclusions could therefore not be drawn from the meta-analyses on most of the following factors: use of rubber dam, canal obstruction & procedural errors, apical size & taper of canal preparation, type of irrigant, type of medicament, root filling material/sealer/technique, and apical disturbance during treatment. The treatment aspects on which reasonable data from previous studies were available included; "pre-obturation culture results", "apical extent of root fillings" "quality of root filling", and "number of treatment visits". The present prospective study therefore aimed to explore some of the previously poorly investigated intra-operative factors. Of all the intra-operative factors investigated, "patency at canal terminus", "apical extent of canal preparation and root fillings", "additional use of 0.2% chlorhexidine or 17% EDTA as canal irrigant", "coronal/canal perforation", and "inter-appointment pain or swelling" were found to have significant influence on success of primary and secondary root canal treatment. Others factors: "operator experience", "protection of the tooth with a metal band during treatment", "use of magnification", "type of instruments for canal enlargement", "size and taper of canal preparation", and "techniques for and quality of root fillings", were found to have no prognostic value.

Although the educational and experience background of the operators had no significant influence on their respective success rates in previous individual studies, the estimated pooled success rates for primary root canal treatment carried out by endodontists or postgraduates were higher than for other dentist groups. In complete contrast, a reverse trend was found with the lowest pooled success rate for secondary root canal treatment by specialists. This discrepancy may possibly be attributable to specialists managing more complex biological or technical problems, perhaps involving perforations, blockages, separated instruments or persistent infections. As the studies did not report on these factors, this supposition could not be tested in the meta-analysis. The present prospective study revealed slightly different but interesting trends that were not statistically significant. There was no difference in success rate between primary and secondary treatment when performed by staff members or 2nd year postgraduate students. Secondary treatments provided by 1st year students had 4% lower success rate. Regardless of type of treatment, staff members achieved the highest success rates. When comparing 1st and 2nd year students, the former achieved higher success rates for primary treatments but lower success rates for secondary treatments. Closer inspection of the data did not reveal any difference in morphological tooth type or pre-operative periapical status in primary treatment performed by the two groups of students (*Results not shown*). There did appear to be a tendency to allocate cases with complex canal anatomy or severe canal curvatures to 2nd year students but the criteria for defining case complexity are still under development within the Endodontic Unit. It may therefore be inferred that the relatively inexperienced 1st year students did not manage secondary treatment cases as effectively as more experienced clinicians. These observations concur with the important influence of the clinical background of operators on the technical outcome of endodontic procedures, demonstrated in laboratory studies (Gulabivala *et al*. 2000, Van Zyl *et al*. 2005). Clearly technical skills play an important role but there is a lack of appropriate tools or methodology to objectively quantify operator skills. The role of such refined technical skills must surely be balanced against the overall understanding of the problem and crucially the motivation and integrity with which the procedure is performed.

Three of the intra-operative factors (“protection of the tooth with a band during treatment”, “use of magnification”, “location of additional canal”), which have never been investigated previously, were all found to have no prognostic value in the prospective study. A band (orthodontic or copper band) was used to facilitate tooth isolation, to support temporary filling and to protect the tooth from fracturing during treatment when one or more cusps were missing or the remaining walls were thin (Gulabivala 2004). Although this practice did not significantly influence the success of treatment, it still improved the outcome of treatment to some extent (OR = 1.19 – 1.48).

The value of magnification during root canal treatment has been repeatedly reinforced by endodontists (Patel & Rhodes 2007) but the present study revealed insignificant benefit to final outcome. Although use of the microscope assisted location of the second mesio-buccal canal in 18–64% of maxillary molars, there was only a small difference in the success rates of mesio-buccal roots with or without a second canal being treated when a periapical lesion was present (Table 3.5.14, page 171). Although, the real benefit of the use of a microscope could only be verified in a randomised controlled trial, the suggestion is quite strong that it would not have a significant impact on the critical apical infection. It was only possible to compare the outcome of roots with additional canals “found or treated” and additional canal “not found”. It was possible that there was actually no second canal in the “not found” group. The counter-argument is that a second mesio-buccal canal has been shown to be present in 95% of extracted maxillary molars (Kulild & Peters 1990). Although clinicians were requested to record “possible missed canal” in each root, examination of the post-obturation radiograph revealed the entries were not consistently accurate. Thus this factor was not analysed. The inaccurate entries were not surprising as the precise information for this could only be obtained from 3D cone-beam tomography in a clinical setting. The lack of negative impact of “additional canal not found/treated” may be due to the transverse anastomosis which allows penetration of irrigant from the “treated” canal into the “untreated but present” canal.

Factors related to mechanical preparation of canals (“type of instrument”, “patency at canal terminus”, “apical size”, “taper and extent of canal instrumentation”) which affect canal cleaning, have again been poorly investigated in the previous studies. Of the five factors analysed in the present prospective study, “patency at canal terminus” and “apical extent of canal instrumentation”, which measure the apical extent of canal cleaning were found to be significant prognostic factors for treatment success. These findings were in agreement with the reports by some previous studies which showed that teeth with canals inaccessible towards the apex were associated with significantly lower success rates (Strindberg 1956, Engström *et al.* 1964, Sjögren *et al.* 1990). In contrast to Sjögren *et al*. (1990), the present study which had similarly large sample sizes for both primary and secondary treatments, did not find any difference in the effects of these two factors on the success of the two treatments (primary and secondary). The adjusted odds ratio for “apical extent of canal preparation” revealed by the present prospective study (OR = 0.87) was almost identical to the odds ratio of 0.86 (*adjusted for periapical status and density of root filling*) reported by Chugal *et al*. (2003).

The present investigation of the influence of type of instrument used for canal enlargement was confounded by the protocol adopted for teaching technical skill as mentioned in the “Materials and Methods” section. The better success rates for hand or rotary NiTi instruments revealed in this prospective study correlate with those clinicians who had already acquired better technical skills to gain and maintain apical patency as well as to avoid procedural errors, an observation also made by Pettitte *et al*. (2001). This, as explained previously, is because the gaining of tactile root canal preparation skills was achieved through the use of stainless steel instruments first. Once students showed proficiency with stainless steel instruments, they graduated to using NiTi instruments. More importantly, such senior students may also have had a better understanding of the biological rationale for root canal treatment. The investigation of the influence of the apical size of preparation was again confounded by the departmental protocol that all canals should be prepared to a minimum ISO size 30, except for cases with very acute or double curvatures. The apical size of preparation was also confounded by the initial apical size of the canal because no further enlargement was carried out in those canals with initial apical size 30 or larger. The success rates were lower for those cases with apical sizes larger than 30. Although this observation was not statistically significant, it was consistent with observations made by Strindberg (1956) and Hoskinson *et al*. (2002). It could be speculated that canal preparation to larger apical size compromises the treatment success by generating more dentine debris, which in the absence of an adequate irrigation regime serves to block canal exits that may still be contaminated with bacteria. Continued generation of dentine debris, in the absence of irrigant, leads to what is termed “dentine mud” which ultimately creates a blockage. The impatient and skill-free clinician is then tempted to force the instrument back to length resulting in procedural errors (apical transportation). Alternately, the initially large canal renders cleaning of the apical portion less effective, but the mechanism for this is not precisely understood. The study findings therefore do not concur with views that more effective bacterial debridement may be achieved with larger apical preparations [(Parris *et al*. 1994, Rollison *et al*. 2002, Card *et al*. 2002)].

Investigation of the influence of canal preparation taper was confounded by the initial size of canal and type of instrument used. Controlled use of stainless instruments as taught on the Masters programme, help create .05 (1 mm step back) or .10 (0.5 mm step back) tapers, although, of course, uncontrolled use could create any shape. Whereas .04, .06, .08 tapers would generally be achieved by canal preparation using greater taper NiTi instruments. The taper of .02 was usually adopted for initially wide open canals. Meaningful comparison could therefore only be made between .05 and .10 tapers created by stainless steel instruments; a negligible difference in success rates was found.

Collating the above results, it could be inferred that it is not necessary to over-enlarge the canal, a preparation size of ISO 30 with a .05 taper for stainless steel instrumentation or .06 taper for NiTi instrumentation is more than adequate. Exactly what, “adequate” means in this context is more difficult to define. Although a number of laboratory studies [(Allison *et al*. 1979, Lee *et al*. 2004, Huang *et al*. 2008)] have investigated the interaction between canal dimensions and irrigation dynamics or obturation dynamics, the precise physical, chemical or biological mechanism that ultimately enable periapical healing remain unknown. There is a need to initiate a cycle of laboratory experiments and clinical trials to identify the optimum balance between canal preparation dimension and irrigation protocol in order to conserve root dentine but achieve effective biofilm removal to facilitate periapical healing.

Given that mechanical instruments only plane about 60% of the canal surface (Mannan *et al.* 2001, Peters *et al.* 2001), the perceived role of canal preparation has undergone a shift from one fulfilling a prime debriding function, to one regarded more as a radicular access for irrigant, dressing and root filling materials to the complex root canal systems (Gulabivala *et al.* 2005). Currently available evidence to guide selection of canal irrigant and dressing material by the clinician is weak. Although the present study was not a randomized controlled trial, it revealed some very interesting findings on some effects of irrigant that have never been previously reported. Whilst the use of a higher concentration of sodium hypochlorite made a negligible difference to treatment outcome, the additional use of some specific irrigants was found to have a significant influence on success rates. The lack of improvement in periapical healing with the use of higher concentration NaOCl solution was consistent with the findings in previous clinical/microbiological studies (Byström & Sundqvist 1983, Cvek *et al.* 1976b). Comparing 0.5% or 5.0% NaOCl solution for irrigation, they found that concentration did not influence the proportion of teeth "rendered culture-negative" (Byström & Sundqvist 1983) or periapical healing (Cvek *et al.* 1976b). As iodine and sodium hypochlorite are both halogen-releasing agents and both attack key groups of protein (McDonnell & Russell 1999), the finding that the additional use of 10% povidone-iodine for irrigation had no additional influence on treatment success was as expected.

Surprisingly, the additional use of 0.2% chlorhexidine solution for irrigation was found to reduce the success of treatment significantly. This finding was in complete contrast to previous reports (Waltimo *et al.* 2006, Siqueira *et al.* 2007c, Wang *et al.* 2007) on its equivalent or superior *in vivo* antibacterial efficacy when compared with sodium hypochlorite solution. The use of chlorhexidine as a final irrigant following sodium hypochlorite irrigation had been recommended some years ago (Kuruvilla & Kamath 1998) and was justified on several grounds, including its substantivity in root dentine (Rosenthal *et al.* 2004), relatively low toxicity (Löe 1973) and broad-spectrum efficacy (McDonnell & Russell 1999). Not until very recently, has alternate irrigation with sodium hypochlorite and chlorhexidine solution raised serious concerns because of their interaction product. The interaction product is an insoluble precipitate containing para-chloro-aniline, which is cytotoxic and carcinogenic (Basrani *et al.* 2007, Bui *et al.* 2008). Apart from mutually depleting the active moiety for bacterial inactivation, the precipitate may cause persistent irritation to the periapical tissue, and block dentinal tubules and accessory anatomy, possibly explaining the observed lower success rate when chlorhexidine was used as an additional irrigant.

The findings on the effect of additional use of 17% EDTA solution for irrigation were also new. Its use had little effect on the success of primary treatment (OR = 1.3

[0.8, 2.1]) but had a profound effect on secondary treatment (OR = 2.3 [1.4, 3.8]). The observed synergistic effect of sodium hypochlorite and EDTA had been demonstrated previously in a clinical/microbiological study (Byström & Sundqvist 1985). The long term (≥ 2 years) outcome of their cases stratified by various canal disinfection protocols (only available from Byström's PhD thesis [1986]) did not support their microbiological findings. The success rate for alternate irrigation with sodium hypochlorite and EDTA solutions (67%) was low when compared with the success rate for irrigation using saline (91%), 0.5% sodium hypochlorite (92%) or 5% sodium hypochlorite (86%) solutions (Byström 1986). These outcome data were unexpected as pre-obturation negative bacterial culture was achieved in all cases. However, there were only 11–15 teeth in each group, therefore these results should be interpreted with caution.

The synergistic effect of the two disinfectants has been attributed to the chelating properties of the sodium salts of EDTA. Their roles in root canal treatment have been reviewed by Zehnder (2006). EDTA solution assists negotiation of narrow or sclerosed canals by demineralisation of root dentine and helps removal of compacted debris from non-instrumented canal anatomy. It may also facilitate deeper penetration of sodium hypochlorite solution into dentine by opening dentinal tubules and removing the smear layer from the instrumented surface, and lastly may help detach or breakup biofilms adhering to root canal walls (Gulabivala *et al.* 2005). In secondary treatment cases, the previously instrumented canals may contain *contaminated* debris, smear layer, un-negotiable calcifications or iatrogenic blockages, and lastly contaminated filling materials. The additional use of EDTA irrigation may help by aiding removal of such contaminated materials, and opening up accessory anatomy and blocked canal exits. In contrast, the smear layer and debris generated from instrumentation of previously untreated canals during primary treatment should be accessible to and relatively easily decontaminated by sodium hypochlorite solution alone. This may possibly explain why the success of primary treatment was not significantly improved by additional EDTA irrigation, whilst secondary treatment was.

The present study could not explore the influence of inter-appointment medicament on treatment success because calcium hydroxide was used as a dressing material in most cases, with very few exceptions.

After chemo-mechanical debridement of the root canal, pain or swelling occurred in 18% of cases and was found to significantly reduce the success of treatment in the present prospective study. The rate of occurrence was within the lower end of the range (2–88%) reported previously (Glennon *et al.* 2004). The present finding was in contrast to previous reports (Kerekes & Tronstad 1979, Byström *et al.* 1987, Sjögren *et al.* 1990) where acute "flare-ups" during treatment were found to have no influence on treatment outcome. Considering the relatively low occurrence of inter-appointment pain or swelling, the three previous studies may lack statistical power as their sample sizes (79–849 roots/teeth) were much smaller than the present study (2484 roots / 1452 teeth). The present finding could be explained by the hypothesis that "flare-ups" were caused by extrusion of contaminated material during canal preparation. Such material may elicit a foreign body reaction or (transient) extra-radicular infection, resulting in treatment failure in a proportion of such cases. Alternatively, acute symptoms may be a result of incomplete chemo-mechanical debridement at the first appointment leading to a shift in canal microbial ecology favouring the growth of more virulent micro-organisms and leading to post-preparation pain and treatment failure. The exact biological mechanisms of failure in these cases, however, warrant further investigation.

Apart from absence of pre-obturation signs and symptoms, the indication for obturation has also been provided by negative pre-obturation canal cultures (Frostell 1963). Pre-obuturation culture was putatively designed to detect residual bacteria in the root canal system in the hope that it would be a good predictor for treatment outcome. In reality, it is probably a better measure of the efficacy of bacterial removal from the *prepared part* of the root canal system. It is likely that the infection in the apical anatomy would be better correlated to treatment outcome (Nair *et al.* 2005, Goria *et al.* 2005) but is not easily sampled. Sampling of the prepared canal has been investigated in previous studies but could not be pursued in the present prospective study.

Meta-analyses revealed that pooled success rates for primary root canal treatment on teeth with negative culture were 7% to 13% higher than for those teeth with positive cultures. After excluding those studies that had not partitioned the secondary treatment cases as well as those that had not provided paired sets of data, only 6 studies remained to contribute to the estimation of the combined effect of this factor on outcome of primary treatment. Although the results of both approaches of analyses (estimation of pooled success rates and pooled odds ratio) were in favour of a negative pre-obturation culture result for primary treatment, the effect (OR 1.2; 95% CI 0.95, 1.44; chi-square for heterogeneity 6.1 [5df] P = 0.294) was not statistically significant. This could be attributed to a lack of statistical power. In order to formally justify the exclusion of studies that had not partitioned secondary treatment cases or failed to fulfil the inclusion criteria, the meta-analysis was repeated by including this data (n=14 studies). On doing so, the estimated effect of pre-obturation culture results (OR=1.9, 95% CI: 1.4, 2.7) became highly significant ($P < 0.001$) but the heterogeneity also became substantial 30.7 [13df, $P = 0.004$]. This highlights the dilemma in where to set the boundary between inclusion and exclusion criteria for studies in systematic reviews. The use of strict inclusion criteria may reduce the number of incorporated studies and heterogeneity but also the statistical power in detecting significance of the factor under investigation as well as that of the heterogeneity. Attempts were made to further analyse the effect of culture results by teeth with or without pre-operative periapical lesion, but the pooled success rates and the odds ratios gave contradictory results. This was due to the small number of studies incorporated in the analyses and a large discrepancy in the number of units in each category. This substantiates the adopted principle of triangulation of outcomes through different analytical approaches as having some merit.

When investigating the influence of bacterial culture results on the outcome of secondary root canal treatment, only two studies could be included. Meta-analyses revealed a large but insignificant difference (52%, OR = 4.3) in success rates between those teeth with negative culture and those with positive culture. The difference was reduced slightly (46%) when only teeth with pre-operative periapical lesion were included in the analysis. It may be hypothesized that the lack of significance was attributable to the small sample size since bacterial culture results had a genuine negative impact on success of secondary treatment. The magnitude of impact of this factor on secondary treatment appeared to be much higher than on primary treatment; this may again be due to over-estimation of the results because of the small sample size. Speculating that the result is true, the observation may be explained by difference in the nature of the residual bacteria present [(Gulabivala 2004)].

Apart from bacterial culture results, apical extent of instrumentation and the apical extent of root fillings may also serve as surrogate measures of root canal treatment efficacy. As discussed previously, whilst the majority of previous studies had not analyzed the influence of apical extent of instrumentation, the measure, “apical extent of root filling” was frequently measured. Therefore, in the absence of such information, the “apical extent of root fillings” may serve as a crude and imprecise surrogate measure of the “extent of instrumentation”. The use of the radiographic root apex as the reference point for measuring the apical extent of root filling in previous studies has been criticized because of the poor correlation between the location of this point and the terminus of canal [(Mizutani *et al.* 1992)]. Therefore, the present prospective study used the location of canal terminus (EAL ‘0’ reading) determined by electronic apex locators as the reference point. As different makes of apex locators (Root ZX [J Morita Co, Tustin, CA, USA]; AFA Apex Finder [Analytic Endodontics, Orange, CA, USA]; Elements diagnostic [SybronEndo, Orange, CA, USA]) have been used, minor discrepancies in locating the EAL ‘0’ reading position were inevitable.

Results of meta-analyses revealed that the effect of apical extent of root fillings on primary and secondary treatment outcome was profound and interacted with the periapical status. The two quantitative analytical approaches concurred with intuitive appraisal of findings from individual studies that: teeth with flush root fillings had the highest success rates followed by short and then long root fillings. This was in agreement with the systematic review by Kojima *et al*. (2004) and the results of the present prospective study. Whilst the meta-analyses revealed a smaller and insignificant difference between flush and short root fillings (OR = 1.27 [0.93, 1.73]), the odds ratio adjusted for periapical lesion was found to be larger with a narrow confidence interval from the present prospective study (OR = 2.1 [1.28, 3.33]).

When comparing the flush and long root fillings in primary and secondary treatment cases, the respective combined odds ratios obtained from meta-analyses (OR = 2.3, 2.3) were similar to the odds ratios adjusted for periapical status revealed in the present prospective study (OR = 2.0, 2.6). The results of the meta-analyses stratified by presence or absence of periapical lesion were unfortunately compromised by the substantially smaller number of studies contributing to the data and have to be interpreted with caution. Nevertheless, the results showed that the difference in success rates between teeth with flush and short root fillings was not significant when the teeth were not associated with periapical lesions. In contrast, the difference in success rates between teeth with short and long root filling was not significant when the teeth *were* associated with periapical lesions. These observations were corroborated by the findings from the present prospective study (*Results not shown*).

On the basis of the above findings, it may be concluded that both apical extent of instrumentation and root fillings had significant effects on outcome. The present prospective study revealed that these two factors correlate with each other, consistent with normal clinical practice to fill the canal to the same extent as canal preparation. A single measure "apical extent of root filling" could therefore inform about both the apical extent of canal cleaning, as well as the potential extrusion of foreign materials into the surrounding tissues. Extrusion of cleaning, medication or filling materials beyond the apical terminus into the surrounding tissues may result in delayed healing or even treatment failure due to a foreign body reaction (Yusuf 1982, Nair *et al*. 1990b, Koppang *et al*. 1992, Sjögren *et al*. 1995). Magnesium and silicon from the talc-contaminated extruded gutta-percha were found to induce foreign body reaction, resulting in treatment failure (Nair *et al*. 1990b). An animal study has shown that large pieces of subcutaneously implanted gutta-percha in guinea pigs were well encapsulated in collagenous capsules, but fine particles of gutta-percha induced an intense, localised tissue response (Sjögren *et al*. 1995). This could infer that extrusion of large pieces of gutta-percha should have no impact on periapical healing but the data from the present study did not support such inference. The discrepancy may be attributed to the potential bacterial contamination in the extruded gutta-percha in the clinical case.

In contrast, extrusion of sealer did not seem to affect the success of primary and secondary treatments in the present prospective study, consistent with the findings by Sari *et al*. (2007). The radiographic assessment for presence and resorption of sealer was complicated by the radiolucent property of the basic components and the insufficient sensitivity of radiographic method to detect small traces of it. It is possible that in some cases, the disappearance of extruded sealer may simply be due to resorption of the radio-opaque additive, barium sulphate. In primary and secondary treatment cases where zinc oxide eugenol-based sealer was extruded, it was radiographically detectable in 39% and 65%, respectively on the final follow-up radiographs. The figure for primary treatment was much lower than the previously reported 69% complete resorption of extruded zinc oxide eugenol-based sealer after 4 years (Augsberger & Peter 1990). The larger number of secondary treatment cases with persistent extruded sealer may be attributed to some pre-existing extruded material as well as extrusion together with sealer during canal obturation.

The difference between the effects of extruded root filling and sealer may be explained in several ways: zinc oxide eugenol sealer possesses antibacterial properties, has higher solubility, and is more readily removed by host cells when compared with gutta-percha points. However, the present study did not account for the quantity of sealer extrusion. Subjective impressions formed when assessing the follow-up radiographs were that extruded sealer may delay periapical healing but not affect the ultimate resolution of the periapical lesion. This subjective observation could not be quantified in the present study as investigation of the rate of periapical healing requires regular and frequent (probably quarterly) radiographic monitoring. The intention is to perform such an investigation beyond the reported study.

Another parameter of obturation was the radiographic measure of “quality of root filling”, which could be used as an indicator of the ability of the root filling to prevent root canal system re-infection or as a surrogate measure of the quality of the entire root canal treatment. Unfortunately, the criteria for judging the quality of root fillings have not been well defined in previous studies. Satisfactory root fillings were defined either as having “adequate seal” or “radiographic absence of voids”. This subjective assessment has not been standardized or calibrated, nor tested for variability in assessment by inter- and intra-observer agreement. Nevertheless, meta-analyses on previous data together with critical appraisal of previous individual studies showed that “unsatisfactory” root fillings were associated with significantly lower success rates than those judged “satisfactory”. So perhaps, the intuitively judged crude measure was adequate for the purpose. A similar meta-analysis could not be performed for secondary treatment due to insufficient previous data. Likewise, this factor could not be analysed in the present prospective study because any sub-standard root fillings revealed on post-obturation radiographs were replaced by the clinicians (as part of their training), with very few exceptions (0.5%–13%).

The effect of number of treatment visits has been an on-going controversy, fuelled by debate between specialists arguing for single visit treatment on the basis of cost-effectiveness and business sense against academics and some specialists arguing for multiple visit treatments, based on biological rationale (Spångberg 2001). The main thread of argument for multiple visit treatments is the putative desirability of using an inter-appointment calcium hydroxide dressing for its antibacterial effect and to gauge the initial periapical response before root filling. The results of the two meta-analysis approaches and intuitive appraisal of individual studies showed no significant difference in the success rates between treatments carried out over one or multiple visits. This was in agreement with the reviews by Sathorn *et al*. (2005) and Figini *et al*. (2007). The present prospective study could not analyse the effect of this factor due to the many hidden potential confounders. As mentioned in the "Introduction" section, three randomized controlled trials (Gesi *et al*. 2006, Molander *et al*. 2007, Penesis *et al*. 2008) were published beyond the time frame of the present and the two published meta-analyses. When their data were pooled with those from the other three previous randomized controlled trials (Trope *et al*. 1999, Weiger *et al*. 2000, Peters & Wesselink 2002), the combined odds ratio for single versus multiple visit treatment on teeth with periapical lesions reduced to very close to 1 (OR = 0.94; 95% CI: 0.60, 1.49) as compared with the odds ratio of 1.34 (95% CI: 0.63, 2.88) reported by Sathorn *et al*. (2005). However, the estimated effect after pooling data (n = 284 for single-visit, n = 258 for multiple-visit) from six studies was still imprecise with a very wide confidence interval. This indicates that the analysis still lacks statistical power, and the issue remains unresolved.

4.2.3.5 Post-operative restorative factors

The placement of a coronal restoration after root filling is considered the final step for teeth undergoing root canal treatment. Its importance was supported by the results of the two analytical approaches (meta-analyses) and the present prospective study. They collectively showed that teeth with satisfactory coronal restorations had significantly better periapical healing compared with those with unsatisfactory restorations, regardless of treatment type (primary or secondary). There were, however, discrepancies in the magnitude of the effect revealed by meta-analyses for primary treatment (OR = 1.82; 95% CI: 1.48, 2.25), and for secondary treatment (OR = 3.31; 95% CI: 1.07, 10.30), as well as the overall adjusted effect (OR = 10.73; 95% CI: 3.65, 31.54) revealed from the prospective study. The magnitude of the effect of coronal restoration on secondary treatment may have been over-estimated in the meta-analysis because of the small number of studies available. The extremely profound effect estimated from the present prospective study may be attributed to the criteria for assessing the quality of coronal restorations. Given that one of the roles of coronal restorations is to prevent post-operative root canal re-infection, the criteria for unsatisfactory restoration given in Hoskinson *et al*. (2002) - (discrepancy, discolouration or recurrent caries at the restoration margin or history of de-cementation) - cannot infer coronal leakage when the inner core is still intact. Therefore, the present prospective study adopted a different classification system and definition for unsatisfactory restorations in order to depict obvious and potential coronal leakage more effectively. The two groups of unsatisfactory restorations were: (1) obvious signs of exposed root filling; and (2) potential leakage indicated by marginal defects and history of de-cementation. This may therefore explain the large effect reported from the present prospective study.

Unlike some previous studies (Heling & Tamshe 1970 & 1971, Heling & Shapira 1978, Heling & Kischinovsky 1979, Allen *et al*. 1989, Cheung & Chan 2003, Fouad & Burleson 2003, Farzaneh *et al*. 2004b, Chu *et al*. 2005), the present study found that type of coronal restoration had no significant influence on success of treatment after adjusting the results for other factors. The present finding was consistent with the observation by Chugal *et al*. (2007). They reported that the type of restoration (temporary versus permanent) had no significant influence on periapical healing after adjusting the results by pre-operative periapical lesion. This discrepancy may be attributed to the underlying reasons for delaying the placement of permanent restorations by dentist or patient. The reasons include the fact that: (1) these teeth may be associated with persistent signs or symptoms of persistent apical periodontitis following treatment; or (2) some referring dentists may defer placement of final restoration on teeth with pre-operative periapical lesion until there is radiographic evidence of periapical healing. These factors may explain the different effects of “type of restoration” when determined using logistic regression with or without adjusting for “pre-operative periapical lesion”.

It has often been recommended that it would be wise to provide a sub-seal over the root filling in case of loss of a restoration; the sub-seal would be glass ionomer (GIC) or zinc oxide eugenol cement (Saunders & Saunders 1994a, Hommez *et al*. 2002, Carrotte 2004, Yamauchi *et al*. 2006). The placement of a GIC or zinc oxide eugenol (IRM®) cement lining coronal to the gutta-percha filling and underneath the permanent core in order to provide additional antibacterial coronal seal, was found to have no beneficial effect on treatment success. It may arguable that the analysis for GIC lining was compromised by the small proportion (5–7%) of cases with such lining. The results, however, were conclusive that the use of IRM® base had no effect on treatment outcome because there was a relatively comparable proportion of cases with IRM® lining (39%) and those without (54–56%). The odds ratios (0.92–0.96) were close to 1 with 95% CI of 0.7 to 1.2; this finding has never been reported previously and does not support this practice (Saunders & Saunders 1994a, Carrotte 2004).

On the basis of the above results, the provision of the *good quality* coronal restoration, regardless of type, should be considered as the final part of the root canal treatment procedure along with obturation to prevent post-operative re-infection.

4.2.4 Prognostic factors for success of treatment using tooth survival as outcome measure

Investigation of prognostic factors for tooth survival following root canal treatment was compromised by the low event rate (small proportion of teeth extracted during the study period). A larger sample size or a longer follow-up after treatment in order to achieve a higher event rate may improve statistical power. The latter strategy may however be compromised by a larger drop-out rate at recall.

Previous evidence for prognostic factors predicting tooth survival was weak. Although 19 potential factors have been investigated previously, most have only been analysed by one study, therefore estimations of combined effect were only possible for 8 factors. Meta-analyses of pooled data revealed that only four conditions (non-molar teeth, teeth with 2 proximal contacts, teeth restored with a crown, teeth not functioning as prosthesis abutments) were significantly associated with better survival. Only 2–3 studies contributed data for “number of proximal contacts” and “functioning as abutment”, therefore the results should be interpreted with caution. The present prospective study found 14 significant prognostic factors of which only two factors (number of proximal contacts, type of post-operative restoration) were common with the meta-analyses findings.

4.2.4.1 Patient factors

The combined effects of medical conditions on tooth survival could not be estimated using meta-analysis due to insufficient previous data. The present prospective study found that teeth in patients suffering from diabetes or receiving systemic steroid therapy had a higher chance of being extracted after treatment. The negative influence of diabetes on tooth survival was consistent with the report by Mindiola *et al*. (2006), whilst the influence of steroid therapy had never been reported previously. It may be argued that patients suffering from diabetes were more susceptible to periodontal disease [(Genco & Löe 1993)] or had a lower success rate of root canal treatment [(Fouad & Burleson 2003)], which in turn could be the reason for tooth extraction. Both factors were found to have a significant influence on tooth survival even when they were entered simultaneously into a multivariable Cox regression model. The results could therefore infer that diabetes increases the risk of tooth loss for reasons other than periodontal problems.

4.2.4.2 Tooth morphological type and location

Tooth morphological type may vary in susceptibility to tooth fracture, a common reason for tooth loss after treatment. Although meta-analysis revealed that molar teeth had a higher chance of being extracted after treatment than non-molar teeth, the present prospective study found that tooth *type* had no significant influence on survival. Maxillary premolars and mandibular molars were found to have the highest frequency of extraction with tooth fracture being the most common reason in the present prospective study. This observation was consistent with previous reports on higher incidence of fracture of maxillary premolars and mandibular molars [(Eakle *et al*. 1986, Lagouvardos *et al*. 1989)]. The factors, “proximal contacts” and “terminal teeth” were found to affect tooth survival significantly in the prospective study, but were significantly correlated to "molar teeth". These findings concurred with the results from the meta-analysis and the report by Tan *et al*. (2006). Of the extracted terminal teeth, 68% were fractured, whilst only 38% of the extracted non-terminal teeth were fractured. Similarly, tooth fracture was the reason for extraction in 58% of teeth with one or less proximal contact, compared with 38% of extracted teeth with 2 proximal contacts. These results could be explained by the unfavourable distribution of occlusal force and higher non-axial stress on terminal teeth and those with less than 2 proximal contacts. Other reasons to explain their higher loss rate are: (1) failure of root canal treatment on a terminal tooth may be accepted more willingly as a reason for extraction as these teeth have little perceived aesthetic value; (2) clinicians may be less likely to offer surgical treatment on terminal molar teeth due to difficult access.

4.2.4.3 Pre-operative conditions of teeth

The presence of pre-operative periapical lesions was found to have no significant influence on tooth survival by both meta-analysis of pooled data from three studies and the present prospective study. On the other hand, pre-operative periodontal probing defects of endodontic origin, pre-operative pain and pre-operative sinus, which have the potential to persist on treatment failure, were found to reduce tooth survival in the prospective study. The above observations were consistent with a previous report that the mere presence of a periapical lesion was not a sufficient reason for dentists and patients to opt for active treatment [(Reit & Gröndahl 1988)]. Interestingly, the influence of pre-operative pain on tooth survival changed over time as its effect declined at around 22 months following treatment. This finding may be explained by the fact that pre-operative pain was a predictor for post-operative [(Yesilsoy *et al*. 1988, Albashaireh & Alnegrish 1998)] and chronic persistent [(Polycarpou *et al*. 2005)] pain after root canal treatment. The persistent pain would then alert patients to seek further endodontic treatment or even tooth extraction sooner rather than later after treatment.

The presence of pre-operative cervical resorption and perforation were also found to significantly reduce tooth survival in the prospective study. This was as expected because tooth fracture and re-infection due to leakage are more likely to occur in these cases. In the presence of re-infection, clinicians are more inclined to suggest extraction due to the intuitive perception of poor long-term prognosis of such teeth.

4.2.4.4 Intra-operative factors

Amongst all the intra-operative factors, "no patency at apical foramen" and "extrusion of gutta-percha root filling" were found to reduce tooth survival in the present prospective study. Extraction of teeth with these conditions was more likely to be due to persistent endodontic problem as both of them were also prognostic factors for treatment success based on periapical healing. In the presence of persistent problems and knowing that the treatment objective of cleaning to the canal terminus could not be achieved, patients and dentists may be more likely to opt for extraction sooner than later. This practice might explain the interesting observation that "patency at canal terminus" only reduced tooth loss within 22 months after treatment but not afterwards. In contrast, "extrusion of root filling" did not influence tooth survival until after 22 months post-operatively, although this factor was also a significant prognostic factor for periapical healing. It may be speculated that dentists were more inclined to advise patients to adopt the "wait and see" strategy if the canals had been perceived to be "successfully" cleaned to the apical terminus. Another possible explanation is that extruded root filling may be due to excessive forces used during compaction of gutta-percha resulting in small cracks in the root. In time, these cracks may propagate with occlusal loading, resulting in re-infection or even root fractures. Such late failures may explain the delayed effect of "extrusion of gutta-percha root filling".

4.2.4.5 Post-operative restorative factors

Protection of teeth with crowns or cast restorations did not influence treatment success based on periapical healing although placement of good cores did. In contrast, placement of crowns or cast restorations was found to improve tooth survival in the meta-analyses as well as the present prospective study. This finding may infer that crowns and cast restorations may help reduce tooth extraction by preventing fracture but that the mere placement of a satisfactory core would be sufficient to prevent re-infection after treatment. The use of cast post & core for retention of restoration was found to reduce tooth survival, in contrast with the results of the meta-analysis on previous data (Caplan & Weintrub 1997, Aquilino & Caplan 2002, Caplan *et al*. 2002, Salehrabi & Rotstein 2004). It was found that the use of posts for retention had no significant influence on tooth survival. However, the analysis was not stratified by the type of post & core material. It may be speculated that the presence of post had different effects on anterior and posterior teeth as they are subjected to different directions and quantity of occlusal force. However, the present survival dataset did not have sufficient power to test interactive effects between factors due to the small number of failure events. Meta-analysis revealed that teeth functioning as prosthesis abutments had poorer survival. This finding may be related to the excessive and unfavourable distribution of occlusal stresses on abutment teeth. The present prospective study also found a similar trend but the number of teeth (n = 94) functioning as abutments was too small to demonstrate a statistically significant effect.

4.3 Clinical implications of findings

In summary, there was close similarity in findings between the meta-analysis and the prospective study (*when results were available from both analyses*), confirming that the results from the prospective part of the study were probably sufficiently robust to draw clinical inference.

The meta-analyses and prospective study both revealed that the success rates and their prognostic factors for periapical healing and tooth survival were similar for both primary and secondary root canal treatment. The findings provide strong confirmation that the principles of primary root canal treatment are identical to those for secondary root canal treatment. The sole difference lies in the potentially compromised access to the apical infection, either due to iatrogenic errors in canal preparation or inability to fully negotiate canal blockages due to natural or artificial materials. The outcome of both treatments should therefore be similar as long as access to the apical infection can be re-established. There is therefore a need for clinicians to acquire the skill to diagnose and correct procedural errors as well as to prevent the introduction of further iatrogenic errors during secondary treatment. The acquisition of such skills must of necessity include the tactile skills necessary to manipulate stainless steel instruments back into previously patent (but now obstructed and deviated) canal termini. Nickel-titanium instruments, lacking the necessary physical properties to be appropriately pre-curved at the tip for re-direction, more often than not prove unsuitable for the task. This may have important implications for the training of clinicians.

4.3.1 Clinical implications based on prognostic factors identified for absence of clinical and radiographic signs of periapical disease

The most powerful impact on root canal treatment success was provided by the pre-operative periapical condition, coded by the prognostic factors “absence of periapical lesion”, “small rather than large lesion” and “absence of sinus tract”. The biological implications of these prognostic factors have already been discussed and suggest that the nature of the host/microbial interaction plays a significant role in the response to treatment. The occurrence of intra-operative pain or swelling also had a significantly negative influence on treatment outcome, which again may be part of this constellation of host/microbial interactions. Specific strategies for predictably preventing, the acute phase manifestation of periapical disease, are not readily available at present and require development through clinical/biological studies. The development of diagnostic tests for identifying susceptible individuals may be a desirable goal, but much preliminary laboratory work still needs to precede such translational research.

Given that these pre-operative prognostic factors are *presenting conditions*, the clinician has little option but to counsel the patient about their prognostic influence. Where a pulpal problem is detected with the potential for progression to a periapical lesion in the future, early pulp extirpation may pre-empt and prevent the development of a periapical lesion (a negative prognostic factor). The problem with this strategy lies in the lack of availability of adequate diagnostic aids in accurately gauging the pulpal and incipient periapical condition. Development of such aids may widen the opportunities for choosing earlier intervention, if indeed such early intervention is deemed appropriate.

The management of the traumatised tooth with a non-responsive pulp raises some questions, particularly in the absence of any evidence for periapical disease. The clinical presentation may either represent a necrotic but un-infected pulp or a vital but concussed pulp. Necrotic pulps without periapical lesions may remain "periapical disease-free" for upto 4–6 years as long as bacteria do not invade the root canal system (Bergenholtz 1974). The impact of the injury may result in micro-cracks in the crown (Love 1996), which may potentially serve as portals of entry for bacteria to cause periapical disease at some point in the future. The International Association of Dental Traumatology recommends annual monitoring for 5 years (Flores *et al.* 2007) to provide root canal treatment as soon as signs of apical periodontitis appear.

The biological inferences of the *treatment*-related prognostic factors have already been discussed; the age-old debate about technical skill versus biological understanding of the problem has been raised once again. Yet it is clear that this problem is not one that can be satisfactorily managed through the adoption of one or the other philosophy alone. It requires the integrated synthesis of both approaches for optimal patient management. Given the significant influence of "patency at apical terminus", "instrumentation to canal terminus", "tooth/root perforation" and "gutta-percha root filling extending to apical terminus without void or extrusion", the clinician's ability to control these elements through satisfactory clinical and technical skills is crucial. The practical inference is that the main focus should be on obtaining and maintaining access to the apical anatomy and its infection during canal preparation, particularly in the presence of a pre-operative periapical lesion or sinus. Given that all of the above factors are technical-skill-dependent, there is a need for clinicians to develop the requisite skills through suitable hands-on coaching. The uniqueness of the skills in endodontics is that these tactile skills must be applied "blindly" to a substrate surface that cannot be directly seen, although some claim the dental microscope to overcome this problem. Together with these manual technical skills, should go three-dimensional mental visualisation skills and the ability to use such visualisation to aid negotiation of the unseen root canal system. The scientific and technical acknowledgement of the need for systematic development of such skills is lacking despite some crude attempts to do so (Gulabivala *et al.* 2000). The need for manual dexterity is essential for developing the tactile skills to: (1) detect canal curvature and aberrations; (2) negotiate fine canals past natural or iatrogenic canal curvatures and natural or foreign materials; (3) maintain canal patency, length and curvature during preparation;

(4) accurately gauge canal diameter, with or without preparation; and (5) control apical placement of root filling material. It is probably for this reason that the epidemiological data suggests that root canal treatment is probably the only surgical procedure with such a high rate of technical outcomes that do not meet guideline standards (Kirkevang *et al.* 2000, Loftus *et al.* 2005). The first challenge is to ensure that undergraduate dental students receive an appropriate grounding in the basic knowledge and technical skills. The latest ESE undergraduate curriculum guidelines for Endodontology (European society of Endodontology 2001) have stipulated a competency-based approach to training, where the trainees are required to demonstrate satisfactory non-surgical root canal treatment including a list of routine procedures. The competencies do not, however, appear to be informed by precise outcome measures and nor are they sub-classified into their component parts to serve as measures of progress or adequate skill. Having graduated with basic competencies, the qualified dentist must consolidate that skill and knowledge base; yet the data shows that many graduates practice procedures that were not taught at the undergraduate level (Jenkins *et al.* 2001). Means need to be found to encourage dentists to continue along the correct path of development. The data from the present study showed some influence of level of qualification and skill on the outcomes; however, as all the clinicians were graduated dentists with a known bias towards endodontics, the sample was too biased to judge the influence of skill properly.

The most powerful treatment prognostic factor emerges as the length to which the root canal system is prepared and obturated. The precision required is underlined by the fact that it is not simply a matter of reaching the canal terminus, for if it was, the clinician could simply over-extend to ensure the apical terminus was reached. The need for precision is reinforced by the negative influence of over-extension beyond the terminus. The difficulty of the task is compounded further by multiple (and unknown) apical canal exits, as well as the changing length of the canal as it is prepared. In the past, estimates of the canal length from various clinical guides had to suffice, whilst today, the process may be informed by electronic apex locators (EAL). Clearly, methods that improve the clinician’s ability to read the canal anatomy and length throughout canal preparation would be a significant advance in treatment methodology.

Maintaining patency at the canal terminus is not simply a matter of negotiating a file to length but to ensure that sufficient antibacterial fluids reach the canal exit to remove, through the coronal opening, any residual infected pulp tissue, bacterial biofilm remnants and dentine debris. This requires suitable root canal irrigation regimes, an area of endodontics that is not currently well served by adequate scientific studies. At least the problem appears to have been recognised and many additional studies have emerged, evaluating the inter-relationship between the canal preparation shape and fluid dynamics. Yet the problem remains unresolved as shown by the outcome of the study from Nair *et al.* (2005). It is interesting that the findings of this latter study had been predicted some years in advance based on the clinical outcome data on the interaction between length of root filling, presence of apical periodontitis and culture test results. The ESE quality guidelines (European society of Endodontology 2006) for root canal treatment stipulate that the objective for canal preparation is to reach as close to the apical constriction as possible. Given the strength of this prognostic factor, and despite the fact that guidelines seek to be broad rather than specific, the requirement for obtaining and maintaining patency at the apical terminus determined by EAL "0" location may be worthy of addition to the guidelines. However, this would need to be balanced by the need to control the placement of root filling material with equal precision, without extrusion (discussed further later).

The important physical effects of irrigants and irrigation need to be viewed alongside their chemical effect, which was evident through the significant beneficial effect of the additional use of EDTA for irrigation, particularly in secondary root canal treatment. It was also evident, albeit in a negative way, since the additional use of chlorhexidine solution with NaOCl for canal irrigation compromised the outcomes. The present study did not investigate the use of chlorhexidine as a sole irrigant and could not comment on its effect on treatment outcome.

EDTA was generally used as a penultimate irrigant followed by a final rinse of NaOCl. The chelating effect of EDTA may help to negotiate the canal by demineralisation of pre-existing natural or iatrogenic canal blockages. After canal enlargement, the use of EDTA may help release contaminated material remaining compacted in accessory anatomy or dentinal tubules and therefore facilitate their decontamination by the final NaOCl rinse. The optimal protocol for irrigation using these solutions, however, remains to be defined, as it is also important to remember that alternate use of NaOCl and EDTA may have a weakening effect on the dentine and teeth (Sim *et al.* 2001, Rajasingham *et al.* 2003).

Another factor that may weaken teeth is injudicious or uncontrolled removal of dentine during access or canal preparation, sometimes leading to tooth perforation, another prognostic factor having a negative effect on outcomes. Clearly again, a balance has to be struck between sufficient dentine removal to provide good mechanical and fluid access for debridement and over-removal that would compromise the tooth. Controlled dentine removal for access again hints at the operator possessing sufficient spatial awareness and hand-piece control for appropriate orientation and steadiness of hand to obtain access without perforation. There are various clinical guides, tips and adjuncts to facilitate proper cavity preparation but innate developed skill is necessary in the specialist and this skill must be acquired by training with the help of a suitable coach. Although the use of a microscope is often touted as a method for precise work, the author's experience through teaching postgraduates is that poorly developed orientational and handpiece control skills tend merely to be magnified with a microscope, producing even more spectacular iatrogenic problems. There is much to be said for systematic training to gradually scale up technical skill levels through properly established foundations. The pursuit of broken instrument or foreign material removal should be tempered by the wisdom of an all-sided evaluation of the case. All too often, the endodontist, focussed down a microscope can lose sight of the overall treatment goal for a tooth, longevity. Iatrogenic errors may be avoided by pursuing alternative options such as surgery. The ability to make such wise choices is dependent upon clinical experience, which demands exposure to a suitable case-mix under supervision. The question is whether such experience should be gained before or after graduation, if the latter, then whose responsibility should it be to provide such training. The current undergraduate curriculum guidelines (European society of Endodontology 2001) do not stipulate minimum case-number and case-mix requirement for gaining competency.

Extending the discussion to the removal of dentine during canal preparation, the endodontic discipline has evidenced the "endodontic guru" sway fashion (practice of their followers) toward large or even small canal tapers. On the basis of the current findings, given that taper of canal preparation has no significant effect on periapical healing; a smaller preparation taper compatible with sufficient root canal irrigation and obturation may be preferable.

Returning to the discussion on obturation length control; the negative impact of under- or over-extended root fillings *also* infers the requirement for developing operator skills and strategies for controlling precise placement of root filling material to the canal terminus without extrusion. Such strategies will invariably include: (1) precise determination of canal terminus location; (2) maintaining the working length or monitoring its change through preparation; (3) avoiding large apical preparations; (4) taking an impression of the apical anatomy with chloro-dipped master gutta-percha cone to gauge the canal complexity and presence of apical resorption; (5) proper customisation of the master gutta-percha cone to ensure a good fit, at least in the apical 3-4 mm; and (6) using controlled exertion of pressure rather than use of excessive, uncontrolled apical forces during root filling compaction.

The resistance to root filling extrusion reduces with the size of apical preparation, therefore over-enlargement of the canal terminus should be avoided. This is consistent with the ESE guidelines, which state that the apical constriction should be maintained in the prepared canal. In addition, the apical size of canal preparation was found to have no influence on periapical healing, supporting the notion that it is not necessary to enlarge the canal unnecessarily. This also contradicts the view amongst some clinicians that larger apical preparations enable better bacterial debridement and would therefore promote better periapical healing. Ultimately, if it is deemed necessary to enlarge the canal terminus to a large size, the control of such an apical preparation, particularly around a curve, is of necessity skill-dependent. Furthermore, tactile skill is also required for accurate gauging of the canal with and without preparation.

Although the literature on canal obturation protocols are replete with methods to check the fit of master gutta-percha cones, including checking for "tug back" or the "cone-fit" radiograph, these methods do not take account of the fact that the apical portion of the prepared canal may be irregular in cross-sectional shape. The use of chloroform for customisation of the master gutta-percha cone, regardless of root filling technique, is the single most predictable way to reduce root filling extrusion (Van Zyl *et al.* 2005). Confirming the need for tactile skill, "Operator" emerged as the most significant factor affecting the proportion of root filling extrusions in their study despite the proposed adoption of a standardized protocol. The ability to control accurate placement of root filling therefore requires specific tactile/manual skills. The study also found that the use of customisation of master cone with cold lateral compaction of gutta-percha resulted in a lower proportion of extruded root fillings, regardless of the operator's training and clinical background. Therefore it may be more appropriate to use this technique while acquiring the requisite tactile skills.

The positive influence of satisfactory quality of root filling revealed from the meta-analysis infers that poorly compacted root fillings detected on the post-obturation radiograph, should be replaced. Yet, this would appear to be rarely practiced, based on epidemiological studies. A number of methods are available to improve the quality/density of root fillings such as the use of customised master gutta-percha (Van Zyl *et al.* 2005) and various thermoplasticised gutta-percha obturation techniques for "back-filling" (Schilder 1967, Buchanan 1996, Bailey *et al.* 2004). Although the ESE guidelines stipulate that "no space should be seen between canal filling and canal wall", and that "there should be no visible canal space beyond the end-point of the root canal filling"; the guidelines do not specifically caution against the extrusion of root filling material into the periapical tissues. Since root filling extrusion is such a powerful prognostic factor for periapical healing, perhaps the current guidelines should be refined to reflect this.

The significant effects of the quality of the coronal restoration warrant its placement as soon as possible after completion of obturation, consistent with the ESE guidelines (2006). Where there is doubt about the future role of the tooth, or about its outcome in the post-treatment review period, at least some sort of a permanent (antibacterial) seal in the access cavity should be placed.

4.3.2 Clinical implications based on prognostic factors identified for tooth survival

Some prognostic factors for tooth survival were common with those for periapical healing, including "sinus tract", "absence of pre- and intra-operative tooth perforation", "achievement of patency at canal terminus" and "absence of root filling extrusion". This suggests that lack of periapical healing affects tooth survival.

Patients suffering from diabetes or receiving systemic steroid therapy *were not* associated with a lower chance of periapical healing but *were* associated with a higher hazard of tooth loss after root canal treatment. Closer inspection of the data revealed that over 50% of such teeth were extracted due to persistent pain. Some of these observations may be explained by the presence of neuropathy, a debilitating painful complication of diabetes (Edwards *et al.* 2008). It is further, interesting to note that systemic steroid therapy is usually prescribed to control such chronic pain (Colman *et al.* 2008, Depalma & Slipman 2008, Kalichman & Hunter 2008). This explanation is consistent with the finding that presence of pre-operative pain significantly increased the hazard of tooth loss.

The negative impact of pre-operative pain on outcome, highlights the importance of accurate pain diagnosis. In some instances, the pain may be of non-endodontic origin, and therefore persists after root canal treatment, despite absence of periapical disease (Polycarpou *et al.* 2005). In other instances, pre-operative pain of endodontic origin may persist following treatment, as a result of peripheral or central sensitisation. Therefore effective pain diagnosis and management for patients presenting with pre-operative pain or the above two medical conditions are crucial.

The pre-operative prognostic factor for tooth survival, “periodontal probing defects” was diagnosed as being of endodontic origin, as it fitted the probing profile of being deep, narrow and localised. Closer inspection of the data on this category revealed that approximately 70% of such teeth were extracted due to tooth or root fracture. It may therefore be speculated that many of the teeth with such periodontal probing profiles were associated with a pre-operative undiagnosed crack. Diagnostic tools such as 3D cone-beam tomography may be useful for detecting such problems to allow appropriate treatment decisions.

Cervical resorption was also a negative prognostic factor for tooth survival. The extent of cervical resorption may influence the risk of tooth fracture as well as compromise effective coronal seal. The data revealed that most of such teeth were extracted due to clinical signs and symptoms of apical periodontitis. This observation reinforces the clinical perspective that achieving an effective coronal seal in such large multi-surfaced cavities is challenging. Therefore, either more effective coronal sealing is required or a concession that such teeth are doomed to failure and better off extracted earlier in the treatment planning.

Teeth restored with cast restorations were found to survive longer, both in the meta-analysis and the prospective study. However, neither analysis was able to investigate the inter-relationship between tooth morphological type, the amount coronal tooth tissue loss after treatment and the type of final restoration. Although the direct and injudicious clinical inference from the result is that cast restorations should preferably be placed on all teeth after root canal treatment, this is probably a gross exaggeration of the true need. Fabrication of a full coverage cast restoration requires further removal of tooth tissue from an already weakened tooth. On the basis of the findings by the two previous studies (Reeh *et al.* 1989, Nagasiri & Chitmongkolsuk 2005), as well as the present findings, posterior teeth with compromised marginal ridges (mesially and/or distally), together with evidence of heavy occusal loading evidenced by faceting, may benefit from cast cuspal coverage restorations. The restoration design should attempt to preserve as much remaining tooth tissue as possible; the implication is that the so-called non-aesthetic but technically demanding partial veneer onlays and partial coverage crowns would be the restorations of choice for root treated teeth. In anterior teeth, the missing tooth tissue may often be replaced with plastic adhesive restorative material. A crown is only indicated when intra-radicular retention is indicated. Although, teeth restored with cast post & core retained restorations were found to a have higher hazard of tooth loss, only 12% of the extracted teeth with cast post & core were incisor or canine teeth. Therefore, the use of such retention should be avoided in premolar and molar teeth only. Alternative treatment options should be considered for severely broken down molar or premolar teeth. When restoring molar teeth, teeth with one or less adjacent teeth, and terminal teeth, it is important to ensure favourable distribution of occlusal forces when designing restorations. If possible, root treated teeth should be avoided as abutments for prostheses or teeth providing occlusal guidance in excursive movements.

4.4 Further studies

It was re-assuring that the critical analyses and subjective intuitive syntheses from individual studies were validated by the formal process of meta-analyses and that these in turn were validated by the findings in the prospective study. Yet, the purist, could easily reject such evidence, regardless of the convergence of the findings from different analyses, on the grounds of lack of formal randomisation of the interventions. From this perspective and to generate the highest levels of evidence, there is a need to perform randomised controlled trials on root canal treatment. This study should form a suitable foundation for launching prioritised and relevant questions for future studies, as well as providing a framework for the nature and extent of data collection required. On-going parallel work has already established an electronic format for such chair-side gathering of data, which should serve the process well. The studies should be targeted at various aspects of the root canal treatment procedure, for which there is scant evidence, including, the interaction between apical size and taper of canal preparation and irrigation protocol (chemical nature, volume, rate and method of delivery, soak-time, mixing, chemical interactions, etc) (Huang *et al.* 2008, McGill *et al.* 2008). The process of debridement should be informed by validated apical sampling of residual bacteria (Goria *et al.* 2003) and methods of gauging the apical canal complexity (Ardeshna *et al.* 2008).

It is evident from the evidence gathered, that despite various improvements in root canal instrumentation and techniques, as well as irrigation protocols, the success of the procedure has not improved over the last century. Whilst surprising at first, this makes absolute sense, when it is considered that all techniques and protocols are capable of debriding the mechanically prepared part of the canal well, but universally fail to directly control the apical residual bacteria (Nair *et al.* 2005). Novel approaches to root canal treatment will therefore need to directly address this problem in a multi-faceted way. The ultimate fate of the residual apical infection is probably dependent on the influence of the treatment protocol on apical infection, the innate resistance of the residual bacterial flora and the influence of the host defence mechanisms. Studies should be designed to specifically evaluate: (1) the bacterial biofilm-removing capacity of irrigation protocols (Spratt *et al.* 2001, Bryce *et al.* 2008); (2) fluid-flow dynamics in the apical anatomy (Huang *et al.* 2008, McGill *et al.* 2008); (3) the nature of the residual bacterial infection in the apical anatomy (Masih *et al.* 2006, Richardson *et al.* 2006, Rojekar *et al.* 2006, Iacovidou *et al.* 2008) and the influence of the apical anatomy on their survival; (4) the role of the host response in controlling the residual infection; (5) the role of the root filling on demise of the residual bacteria; bioactive materials should be considered (Borbely *et al.* 2008). A number of studies have already begun to evaluate these aspects within our group and others are in the process of design.

The present study identified the problem of pre-, intra- and post-operative pain associated with root canal treatment in a small proportion of patients, confirming previous findings (Glennon *et al.* 2004, Polycarpou *et al.* 2005). The problem leads to decision-making dilemmas for patients and clinicians, particularly when high costs are involved. There is therefore a need for further investigation of the cause of such pain. Residual pain in some of the cases was found to resolve spontaneously in a separate on-going study, specifically evaluating this aspect. The outcomes may be better assessed by Cone-beam CT imaging of the periapical tissues. Further studies on management of pain, before, during and after root canal treatment are merited, including the role of the microbial flora, as well as the host mechanisms.

The present study suggested that tooth fracture and restoration failure were two of the most common reasons for tooth loss. Apart from helping to achieve periapical healing, the root canal treatment procedure should ideally incur minimal damage to the remaining tooth tissue. Studies have demonstrated the potential for over-enlargement of the canal, aggressive use of chemical agents and heavy forces during root canal obturation to affect the integrity and strength of dentine and roots (Sim *et al.* 2001, Sathorn *et al.* 2005a, Andreasen *et al.* 2002, Soros *et al.* 2008). Clearly a balance needs to be struck between the need for bacterial debridement and mechanical protection of the remaining tooth tissue. Further *in vitro* studies and long term clinical studies are therefore required to investigate the influence of root canal treatment and restorative factors on long-term tooth survival. The influence of occlusal loading seems paramount but has been little studied in this context and should be followed up further, particularly the influence of proprioceptive mechanisms in the pulp. Considering the low tooth loss events, a longer follow-up duration such as 10 years should ideally be adopted in order to improve statistical power by accumulating more failure-events.

4.5 Conclusions

In general, the results of the meta-analyses and the prospective study were in concordance.

In the prospective study, no clinically significant difference in success rate (measured as absence of periapical disease) was found between primary (83%) and secondary (80%) root canal treatment (adjusted OR = 1.28; 95% CI 0.91, 1.58). This finding was similar to that of the result from the meta-analysis (OR = 1.26; 95% CI: 0.77, 2.07). Using logistic regression (with root as the unit of assessment) and accounting for the clustering effect within patients, the influence of 11 prognostic factors, including three of the four identified from meta-analysis (pre-operative periapical status, extent of root-filling, post-operative restoration quality) was found to be the same for both treatments with one exception, “EDTA as additional irrigant”. EDTA had no statistically significant effect on primary root canal treatment, while its use significantly increased the success of secondary treatment. The quality of root filling was also found to be a significant prognostic factor in the meta-analysis but could not be investigated in the present prospective study.

Combining the results of meta-analyses and prospective study, the conditions that were found to improve success rates of root canal treatment were:

- presence of vital pulp with an absence of pre-operative periapical lesion; when a periapical lesion was present, the smaller its size, the better the treatment prognosis;
- absence of pre-operative sinus tract (**first study to formally report this finding**);
- achievement of patency at the canal terminus (**first study to formally report this finding**);
- extension of canal cleaning as close as possible to the terminus;
- use of EDTA solution as a penultimate wash followed by final rinse with NaOCl solution, after chemo-mechanical debridement using NaOCl solution as irrigant for secondary root canal treatment cases (**previously unreported finding**);
- abstain from using chlorhexidine solution as an adjunct irrigant to NaOCl solution during treatment (**previously unreported outcome finding**);
- absence of tooth/root perforation;
- absence of inter-appointment flare-up (pain or swelling) (**first study to formally report this finding**);
- absence of root filling extrusion;

- root filling without voids (only from meta-analysis); and
- presence of a satisfactory coronal restoration.

The prospective study found the 4-year survival rate of root-treated teeth after primary or secondary root canal treatment to be 95% (95% CI 94%, 97%); this was confirmed by the meta-analyses on primary root canal treatment (93% [95% CI 92%, 94%] for 5-year survival). The meta-analyses identified 4 prognostic factors (pre-operative periapical lesion, crowned tooth, proximal contacts, abutment), whilst the prospective study using Cox regression, accounting for the clustering by patient, identified 14 factors, including two from the meta-analyses. Amongst these 14 factors, “pre-operative pain”, “canal terminus patency” and “extruded root-filling” had different effects on survival before and after 22 months post-treatment.

Conditions that were found to improve tooth survival following root canal treatment were:

- patients not suffering from diabetes or receiving systemic steroid therapy (**first study to report this finding**);
- absence of pre-operative deep periodontal probing defects, pain, sinus tract and cervical resorption (**first study to report this finding**);
- absence of pre- and intra-operative tooth perforation;
- achievement of patency at canal terminus (**first study to report early effect of this factor**);
- absence of root filling extrusion (**first study to report delayed effect of this factor**);
- teeth with cast restoration after treatment;
- teeth with both mesial and distal adjacent teeth present;
- non-molar teeth (only from meta-analysis);
- teeth not requiring cast post & core for support and retention of restoration; and
- teeth not functioning as prosthesis abutments (only from meta-analysis).

Majority of the lesions healed completely within 1 year (72%, 71%) and another large proportion healed completely between 1–2 years (19%, 24%) following primary or secondary root canal treatment, respectively. However, the factors affecting the rate of healing of periapical lesions and the rate of reduction in the size of periapical lesion with 4 years after treatment were not investigated in the present study because such analyses required outcome data obtained from more frequent follow-ups.

In conclusion, the systematic review/meta-analyses of previous data were useful in identifying significant prognostic factors, as well as the deficiencies in the evidence-base. The large sample size, detailed and meticulous data recording, as well as application of appropriate statistical methods in the prospective study allowed a number of clinical inferences (*some previously unreported in the literature*) to be drawn. The findings support the latest ESE guidelines (2006) for root canal treatment as well as provide evidence for its refinement: (1) mechanical patency should be achieved at the canal terminus whenever possible; (2) location of the canal terminus should preferably be determined using an electronic apex locator and confirmed with a radiograph; (3) when patency is achieved, it should be maintained during canal enlargement; (4) the irrigation solution should preferably have disinfectant, organic debris dissolving and *chelating* properties; (5) the alternate/combined use of interacting irrigants should be avoided; (6) root filling material should not be extended beyond the apical terminus.

Although the technical skills inherent in intra-operative root canal treatment were not formally measured, the intra-operative prognostic factors requiring control were all technical-skill-dependent. These aspects should be specifically studied in future studies, particularly from the perspective of training dentists and allowing the relevant skills to be consolidated.

The clinical findings form an interesting and robust platform from which to launch clinically relevant and meaningful questions for biological, laboratory-based studies that could ultimately lead to translational findings for improvement in clinical practice.

Lastly, although the aspect of “intuitive decision-making” was not formally tested against the formal statistical evaluation of the literature, it was an interesting part of the study process, which was repeatedly confirmed by the formal analysis. This gave rise to considerable confidence in the traditional authoritative process of critical analysis and synthesis. The “intuitive process” merits further study.

Chapter 6

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Appendix I

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with ≥ 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:

- EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
- OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
- Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1 - 5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

Appendix II

Protocols for basic canal instrumentation and obturation

Root Canal Preparations

Stepback preparation using filing techniques

1. Take pre-operative radiograph to assess the pulp chamber and root canal anatomy.
2. Prepare access cavity to provide straight line access to the canal orifices using TC #256, Endo-Z bur.
3. Estimate the WL from pre-operative radiograph. Determine working length using # .08/.10 Flex-O-Files and take a radiograph to verify the WL.

4. Apical preparation:
   - Insert the first binding file to full working length without force and file circumferentially until the next size up will just reach the full WL. (***In a curved canal, pre-curved instruments should be used with anti-curvature filing***).
   - Repeat until a size 30 Flex-O-File which is the Master Apical File (MAF) will just reach the working length. *(If the size of the first binding file is larger than 30, the first binding file will be used as the MAF).*
   - Irrigate copiously and maintain patency using patency filing (# .08 or .10 Flex-O-Files) between each new file.

5. Flaring:
   - The preparation is flared using the next larger file 1mm shorter than the previous file until it is "just loose" (up to size 80 Flex-O-File).

6. Take a MAF radiograph after you have finished the preparation.

N.B. The files should be used in a small amplitude push-pull filing motion.

3

Stepback preparation using rotational techniques

1. Take pre-operative radiograph to assess the pulp chamber and root canal anatomy.
2. Prepare access cavity to provide straight line access to the canal orifices using TC #256, Endo-Z bur.
3. Estimate the WL from the pre-operative radiograph. Determine working length using #.08/.10 Flex-O-files and take a radiograph to verify the WL.

4. Apical preparation:
   - Insert the first binding file to full working length without force and file in a stem-winding motion until the next size up will just reach the full WL.

     The file is used with gentle apical pressure and clockwise and counter-clockwise motion as the instrument is advanced. Do not apply increased force if resistance is met. Instead, withdraw the file and clean it, irrigate the canal and try again. If the instrument cannot be advanced further to the estimated WL, then select a smaller size and try again. Use a #08 file to check patency. Repeat this process, cycling between different sizes to negotiate the full length of the canal to size 30.

5. Flaring:
   - The preparation is flared using a larger file 1mm shorter than the previous file until it is just loose (up to size 80 Flex-O-File).

6. Take a MAF radiograph after you have finished the preparation.

5

Stepdown preparation using filing technique

1. Take pre-operative radiograph to assess the pulp chamber and root canal anatomy.
2. Prepare access cavity to provide straight line access to the canal orifices using TC #256 & Endo-Z bur.

3. Coronal preparation:
   - Explore canal anatomy with 0.8 Flex-O-Files to determine the apical extent of the coronal preparation along with the pre-operative radiograph.
   - Prepare the coronal portion of the canal to the beginning of the curve using **Hedstrom files (15-40) in a circumferential filing motion. (Do not force the file when it meets resistance as it may encounter a curve that is not apparent on the radiograph)**

     (Sizes .08 or.10 Flex-O-Files should be used to ensure the canal is not blocked beyond the length of coronal preparation)
   - Use small files (.08 or.10 Flex-O-Files) to establish patency
   - Determine the working length and take a radiograph to confirm the WL.

4. Apical preparation and flaring:
   - Use Stepback technique described previously to complete apical preparation and flaring

5. Take a radiograph with the MAF placed in the canal.

7

Stepdown preparation using rotational technique

1. Take pre-operative radiograph to assess the pulp chamber and root canal anatomy.
2. Prepare access cavity to provide straight line access to the canal orifices using TC #256 & Endo-Z bur.

3. Coronal preparation:
   - Explore canal anatomy with 0.8 Flex-O-Files to determine the apical extent of the coronal preparation along with the pre-operative radiograph.
   - Prepare the coronal portion of the canal to the beginning of the curve using **Flex-O-Files (15-40) in a stem- winding motion**.

     (Sizes .08 or.10 Flex-O-Files should be used to ensure the canal is not blocked beyond the length of coronal preparation.)
   - Use small files (.08 or .10 Flex-O-Files) to establish apical patency
   - Determine the working length with an appropriately sized file and take a radiograph to confirm the WL.

4. Apical preparation and flaring:
   - Complete apical preparation by a stem- winding motion to size 30.
   - Use the stepback technique described to complete flaring

5. Take a radiograph with the MAF placed in the canal.

9

Root Canal Obturation Techniques

Cold lateral compaction

1. Select a spreader that would fit to the full working length.
2. Select a standardised gutta-percha point, matching the master file size that just snags in the apical portion of the canal at the full WL.

   Customizing the master cone to fit the apical portion of root canal:

   - *Select a master cone which is usually 1-2 sizes larger than the MAF and binds 1mm short of the WL.*
   - *Hold the master cone with a pair of locking tweezers at the WL, dip the apical 1mm into chloroform for 1 second and insert it into the slightly moist canal to the WL with a pumping motion until it reaches the WL. Continue to pump for 20 times at the WL to allow the soften tip of the gutta-percha point to become hardened.*
   - *Note the orientation before taking it out of the canal.*
   - *Examine the shape of the tip of the gutta-percha point which should have formed an impression of the apical portion of the root canal. Check the length of the formed gutta-percha point which should match the full WL.*
   - *Allow it to dry for 30s.*
3. Coat the canal wall with sealer carried on paper points (Sealer should be mixed to a viscous consistency).
4. Place the master cone to full WL.
5. Insert the spreader as far as possible and compact the point against the canal wall. (In a curved canal, insert the spreader at the outer curve and compact the gutta-percha against the inner curve.)
6. Leave the spreader in place for a few seconds and remove from root canal by slight rotational motion.
7. Insert accessory cone (matching the used spreader) into the space created by the spreader (Measure the accessory cone to the WL and mark it by notching or bending to help prevent extrusion).
8. Repeat the compaction until the apical 4mm of the canal/apical to the curve is filled.
9. Take a radiograph (i.e. mid-fill radiograph) to check the quality of the apical root filling.
10. Remove the gutta-percha points protruding from the orifice with a hot instrument (heat carrier).
11. Continue with the compaction in the coronal portion. Insert the spreader into the middle of the gutta-percha mass. (It may be possible to use wider tapered spreader/accessory cones.)
12. Seal the gutta-percha 2mm below the orifice using a hot instrument and compact it with a root canal plugger.
13. Take a post-operative radiograph.

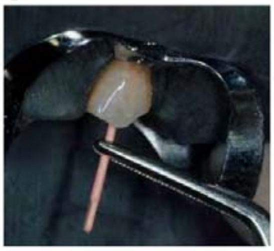
11

Cold lateral compaction technique with customized master gutta-percha cone

1

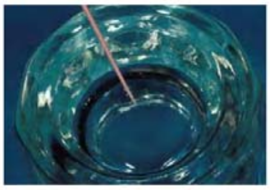
- Select a standardized GP point 1-2 sizes larger than the apical preparation.
- Mark the selected master point at working length.

2



- Gently place the point into the canal.
- Trim the tip until it binds at 1-2 mm short of working length.

3



- Dip 1-2 mm of the tip of point in chloroform for 1-2 seconds, depending on size.

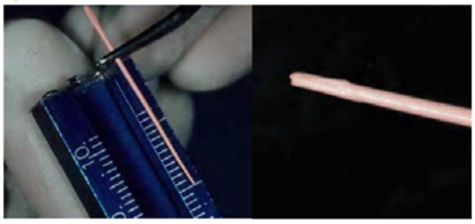
4

- Gently place the softened GP point into the slightly moist canal.
- Note orientation of insertion.
- Pump the GP point towards the working length firmly and deliberately but gently.

5

- Once the working length is reached, keep pumping for another 10 sec to allow the GP point to become firm and to prevent it from engaging any undercut.

6



- Remove the cone from the canal and check the following:
  - Has the GP point buckled?
  - Is the marked length still the same as the working length?
  - Does the tip of the GP point appear to be an impression of the apical anatomy?

7

- Dry canal thoroughly.
- Coat canal wall and tip of GP point with a smear of sealer.
- Insert the GP point into the canal following the previous orientation.
- Seat GP point firmly at the working length.
- Apply gentle apical pressure to the point to check the fitting of the point.
- Complete obturation using lateral compaction technique.

13

Appendix III

Advanced canal instrumentation and obturation techniques covered in the self-directed learning Endodontic technique course

Advanced instrumentation techniques using stainless steel files	**Canal preparation using NiTi instruments**	**Advanced obturation techniques**
1. Double-Flare technique (Fava 1983) 2. Crown-Down Pressureless technique (Morgan & Montgomery 1984) 3. Roane's technique (Roane *et al*. 1985) with balanced force manipulation of instruments (Roane *et al*. 1985) 4. Modified double-flare technique (Saunders & Saunders 1994b)	**Instruments for hand manipulation** 1. File Nitiflex® 2. GT hand files 3. ProTaper® files **Instruments used on automated handpiece** 4. SystemGT® rotary files 5. ProFile® 6. ProTaper® rotary files 7. K3™ Nickel-titanium files 8. LightSpeed system	1. Warm lateral compaction (with Ultrasonic spreading) (Bailey *et al*. 2004) 2. Schilder technique (Schilder 1983) 3. Continuous Wave technique (Buchanan 1996) 4. Thermafil® (Dentsply-Maillefer) SimpliFil® ((LightSpeed Technology, Inc, Maidstone, UK) 5. Thermocompaction techniques a. McSpadden JT. Presentation to the meeting of the American Association of Endodontists, Atlanta, Georgia, USA 1979. b. Tagger hybrid (Tagger *et al*. 1983) c. Alphaseal system (Prestige-dental, Bradford, UK) and stainless-steel gutta-condensors (Dentsply-Maillefer) d. MicroSeal® system with nickel titanium MicroSeal® condenser (SybronEndo)

Transition from Stainless Steel to Rotary Instrumentation Techniques
Teaching/Learning Protocol 2006 (Summary)

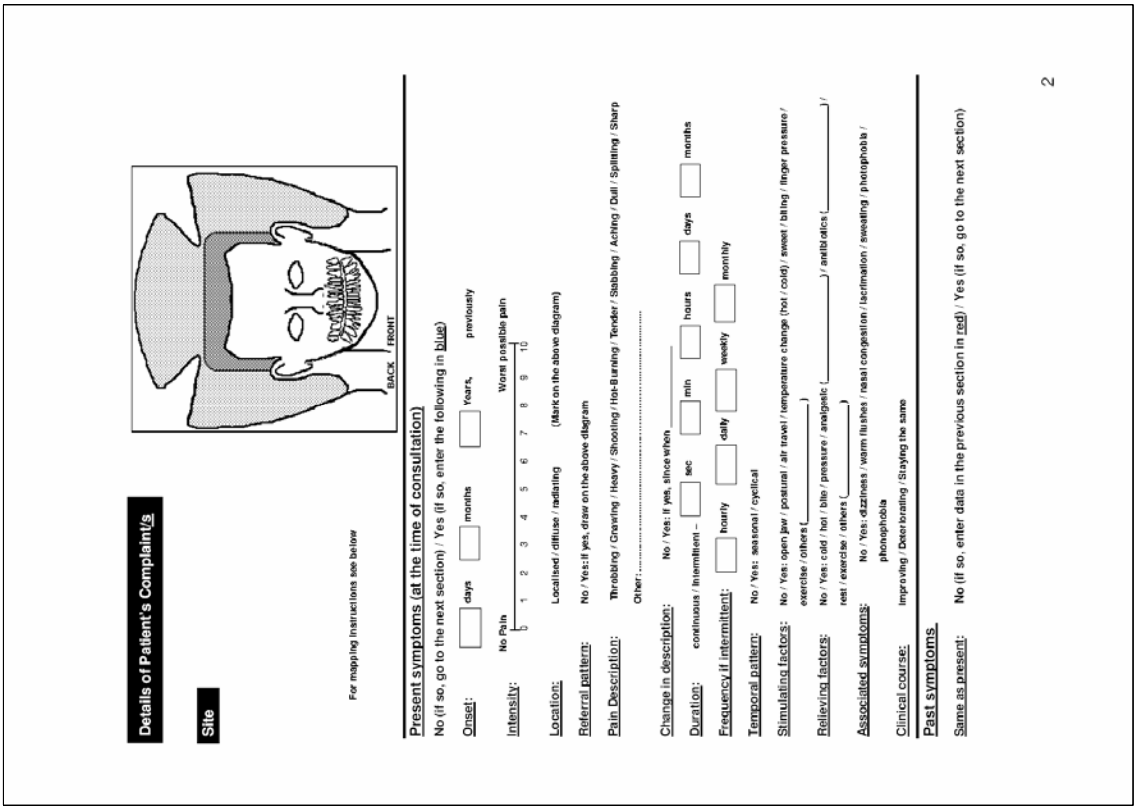
1. **20–30 teeth** prepared using stainless steel files showing consistency in taper and curvature control.

2. **5–10 cases** prepared using hand ProTaper (S1 & Sx) for coronal flaring and stainless instruments for apical and stepback preparation.

3. **5 cases** using each of the following NiTi instrument systems;
   * Hand GT system / Rotary GT system (with transition from hand to rotary);
   * Hand ProTaper system / Rotary ProTaper system (with transition from hand to rotary);
   * Rotary profile (could be preceded by hand option using Implant drill handles);
   * K3 system (could be preceded by hand option using Implant drill handles).

Appendix IV

Endodontic examination form



Details of Patient's Complaint/s

Site

For mapping instructions see below

Present symptoms (at the time of consultation)

No (if so, go to the next section) / Yes (if so, enter the following in blue)

Onset: [ ] days [ ] months [ ] Years, previously

Intensity: No Pain 0 1 2 3 4 5 6 7 8 9 10 Worst possible pain

Location: Localised / diffuse / radiating (Mark on the above diagram)

Referral pattern: No / Yes: if yes, draw on the above diagram

Pain Description: Throbbing / Gnawing / Heavy / Shooting / Hot-Burning / Tender / Stabbing / Aching / Dull / Splitting / Sharp

Other: ....

Change in description: No / Yes: if yes, since when ___________

Duration: continuous / intermittent – [ ] sec [ ] min [ ] hours [ ] days [ ] months

Frequency if intermittent: [ ] hourly [ ] daily [ ] weekly [ ] monthly

Temporal pattern: No / Yes: seasonal / cyclical

Stimulating factors: No / Yes: open jaw / postural / air travel / temperature change (hot / cold) / sweet / biting / finger pressure / exercise / others (______________)

Relieving factors: No / Yes: cold / hot / bite / pressure / analgesic (______________) / antibiotics (______________) / rest / exercise / others (______________)

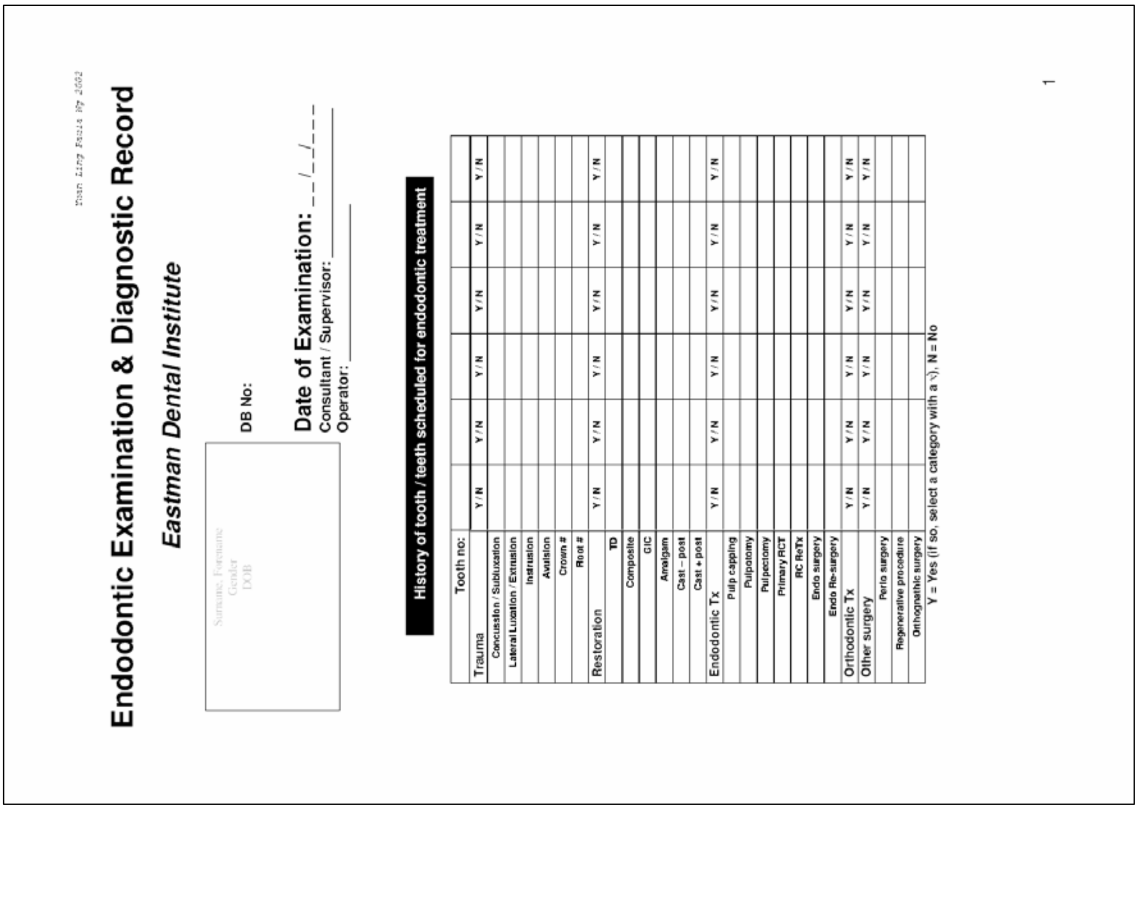
Associated symptoms: No / Yes: dizziness / warm flushes / nasal congestion / lacrimation / sweating / photophobia / phonophobia

Clinical course: Improving / Deteriorating / Staying the same

Past symptoms

Same as present: No (if so, enter data in the previous section in red) / Yes (if so, go to the next section)

2



Yoan Ling Fauia Wy 2002

Endodontic Examination & Diagnostic Record

Eastman Dental Institute

Surname, Forename
Gender
DOB

DB No:

Date of Examination: _ _ /_ _/_ _ _

Consultant / Supervisor: ______________

Operator: ______________

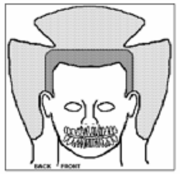
History of tooth / teeth scheduled for endodontic treatment

Tooth no:						
Trauma	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Concussion / Subluxation						
Lateral Luxation / Extrusion						
Instrusion						
Avulsion						
Crown #						
Root #						
Restoration	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
TD						
Composite						
GIC						
Amalgam						
Cast – post						
Cast + post						
Endodontic Tx	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Pulp capping						
Pulpotomy						
Pulpectomy						
Primary RCT						
RC ReTx						
Endo surgery						
Endo Re-surgery						
Orthodontic Tx	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Other surgery	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Perio surgery						
Regenerative procedure						
Orthognathic surgery						

Y = Yes (if so, select a category with a √), N = No

1

Extra - Oral Examination



Swelling No / Yes (if so, complete the following)

- Site: mark on diagram with a circle
- Size: Max. Dimension ________cm
- Consistency: Soft / Firm / Bony / Fluctuant / (Pointing)
- Colour: Blue / Black / Red / Pink / Yellow / Brown / White
- Movement: Mobile / Fixed

Lymphadenopathy No / Yes (enlarged and / or tender nodes)

Submandibular R L / Submental R L / Cervical R L / Pre-auricular R L / Post-auricular R L

TMJ	Right	Left
Clicking	Y / N	Y / N
Crepitus	Y / N	Y / N
Trismus	Y / N	Y / N
Asymmetry	Y / N	Y / N
Tenderness to palpation	Y / N	Y / N

Muscles tender point	Right	Left
Masseter	Y / N	Y / N
Temporalis	Y / N	Y / N
Pterygoids	Y / N	Y / N
Neck	Y / N	Y / N
Shoulder	Y / N	Y / N
Upper back	Y / N	Y / N

Pre-operative status of teeth scheduled for Endodontic Treatment

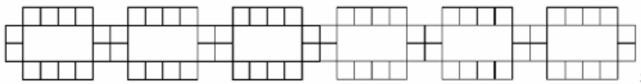
Restorative status

Tooth No:						
Restored	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Cracks	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Fracture	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Caries	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Pulp exposure	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
GP exposure	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Restoration – type	TD/plastic/cast	TD/plastic/cast	TD/plastic/cast	TD/plastic/cast	TD/plastic/cast	TD/plastic/cast
Restoration – post	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Restoration – marginal discrepancy	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N

Pulpal and periapical status (Y = Positive response N = Negative response X = Test not carried out)

Tooth No:						
TTP (Coronal-Apical)	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
TTP (Buccal)	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
TTP (Lingual)	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Soft tissue tenderness to pressure	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Soft tissue swelling (buccal)	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Soft tissue swelling (palatal/lingual)	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Sinus (buccal)	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Sinus (palatal / lingual)	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Mobility (Normal / 0 / 1 / 2 / 3)	Nor/ 0/ 1/ 2/ 3	Nor/ 0/ 1/ 2/ 3	Nor/ 0/ 1/ 2/ 3	Nor/ 0/ 1/ 2/ 3	Nor/ 0/ 1/ 2/ 3	Nor/ 0/ 1/ 2/ 3
Percussion tone (Normal / High)	Nor / Hi	Nor / Hi	Nor / Hi	Nor / Hi	Nor / Hi	Nor / Hi
Cold Air	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x
Cold H_2O	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x
Ethyl Chloride / Endo Ice	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x
Hot GP	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x
Hot H_2O	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x	Y / N / x
EPT (AT score)						
Bite Test (Pres / Rel / Neg)	P / R / N	P / R / N	P / R / N	P / R / N	P / R / N	P / R / N
(+)ve cusp						

Periodontal Pocket Depths



3

Diagnosis / Prognosis of teeth scheduled for endodontic treatment

Tooth no:				
Pulpal diagnosis	WNL Dentine Sensitivity Dentine Hypersensitivity Crack Tooth Syndrome Pulpitis - Rev / Irrev Necrosis - Partial / Total	WNL Dentine Sensitivity Dentine Hypersensitivity Crack Tooth Syndrome Pulpitis - Rev / Irrev Necrosis - Partial / Total	WNL Dentine Sensitivity Dentine Hypersensitivity Crack Tooth Syndrome Pulpitis - Rev / Irrev Necrosis - Partial / Total	WNL Dentine Sensitivity Dentine Hypersensitivity Crack Tooth Syndrome Pulpitis - Rev / Irrev Necrosis - Partial / Total
Periapical diagnosis*	WNL AcuteAP AcuteAA ChronicAP + Suppuration + Acute exacerbation	WNL AcuteAP AcuteAA ChronicAP + Suppuration + Acute exacerbation	WNL AcuteAP AcuteAA ChronicAP + Suppuration + Acute exacerbation	WNL AcuteAP AcuteAA ChronicAP + Suppuration + Acute exacerbation
Other endo. diagnosis	Root Fracture Vert. / Horizon. / Obliq. Resorption – Internal Resorption – ext. surface Resorption – ext. Inflam. Cervical / Mid / Apical Resorption – ext. replace.	Root Fracture Vert. / Horizon. / Obliq. Resorption – Internal Resorption – ext. surface Resorption – ext. Inflam. Cervical / Mid / Apical Resorption – ext. replace.	Root Fracture Vert. / Horizon. / Obliq. Resorption – Internal Resorption – ext. surface Resorption – ext. Inflam. Cervical / Mid / Apical Resorption – ext. replace.	Root Fracture Vert. / Horizon. / Obliq. Resorption – Internal Resorption – ext. surface Resorption – ext. Inflam. Cervical / Mid / Apical Resorption – ext. replace.
Periodontal diagnosis				
Endo Treatment prescribed	Elective RCT Primary RCT RC re-treatment Apicectomy Retro-grade RCT Through & Through surg. Root resection Combined non-surgical + surgical Tx	Elective RCT Primary RCT RC re-treatment Apicectomy Retro-grade RCT Through & Through surg. Root resection Combined non-surgical + surgical Tx	Elective RCT Primary RCT RC re-treatment Apicectomy Retro-grade RCT Through & Through surg. Root resection Combined non-surgical + surgical Tx	Elective RCT Primary RCT RC re-treatment Apicectomy Retro-grade RCT Through & Through surg. Root resection Combined non-surgical + surgical Tx
Endo Prognosis	Good Fair Poor	Good Fair Poor	Good Fair Poor	Good Fair Poor
Perio Prognosis	Good Fair Poor	Good Fair Poor	Good Fair Poor	Good Fair Poor
Rest. Prognosis	Good Fair Poor	Good Fair Poor	Good Fair Poor	Good Fair Poor

*Code for periapical diagnosis: AA = apical abscess, AP = apical periodontitis

4

Appendix V

Root canal treatment form

DB No:

Yuan-Ling Paula Ng

Patient name
Gender
DOB

Root Canal
-Treatment History-

Use a separate form for each tooth treated

Treatment category for each root

Tooth Number	Roots				
Primary RCT					
Patent Canal					
Calcified Canal					
Complex Anatomy					
Internal Resorpion					
Apexification/Apexogenesis					
RC Re-treatment					
Remove Post					
Remove G.P.					
Remove Paste					
Remove/Bypass Ag Point					
Remove/Bypass # instr.					

Department of Endodontics
UCL Eastman Dental Institute

Appointment Record

Supervisors please check before signing

	Date	Operator Initials	Supervisor Initials	Signature
Visit 1				
Visit 2				
Visit 3				
Visit 4				

If 5th visit required, review treatment plan!

Post-treatment evaluation

Were treatment aims achieved? Yes___, No___, Don't know___

Estimated Success Rate by operator: _____ %

Estimated Success Rate by supervisor: _____%

1

General information for each visit

Visit	Treatment	Irrigant Used	Canal Dressing Material	Lubricant used	Temp. Filling	Total Surgery Time	Magnification	Inter-appt. Pain After Visit	Inter-appt. Swelling After Visit	Antibiotic Prescribed After Visit
1	Prep. ____ RD ____ RF ____	NaOCl 2.5% ____ NaOCl 5.0% ____ Iodine 10% ____ CHX ____ EDTA 17% ____	Ledermix ___ Ca(OH)₂ ___ Antibiotics ___ Type _____	None ____ Glyde ____ Fileze ____ Hibiscrub ___	IRM ____ GIC ____ Band ____ Temp Cr. ____ Post ____	___ min	None ___ Loops ___ Scope ___	Yes _____ Intensity__/10 No _____	Yes _____ No _____	Yes _____ No _____
2	Prep. ____ RD ____ RF ____	NaOCl 2.5% ____ NaOCl 5.0% ____ Iodine 10% ____ CHX ____ EDTA 17% ____	Ledermix ___ Ca(OH)₂ ___ Antibiotics ___ Type _____	None ____ Glyde ____ Fileze ____ Hibiscrub ___	IRM ____ Band ____ Temp Cr. ____ Post ____	___ min	None ___ Loops ___ Scope ___	Yes _____ Intensity__/10 No _____	Yes _____ No _____	Yes _____ No _____
3	Prep. ____ RD ____ RF ____	NaOCl 2.5% ____ NaOCl 5.0% ____ Iodine 10% ____ CHX ____ EDTA 17% ____	Ledermix ___ Ca(OH)₂ ___ Antibiotics ___ Type _____	None ____ Glyde ____ Fileze ____ Hibiscrub ___	IRM ____ Band ____ Temp Cr. ____ Post ____	___ min	None ___ Loops ___ Scope ___	Yes _____ Intensity__/10 No _____	Yes _____ No _____	Yes _____ No _____
4	Prep. ____ RD ____ RF ____	NaOCl 2.5% ____ NaOCl 5.0% ____ Iodine 10% ____ CHX ____ EDTA 17% ____	Ledermix ___ Ca(OH)₂ ___ Antibiotics ___ Type _____	None ____ Glyde ____ Fileze ____ Hibiscrub ___	IRM ____ Band ____ Temp Cr. ____ Post ____	___ min	None ___ Loops ___ Scope ___	Yes _____ Intensity__/10 No _____	Yes _____ No _____	Yes _____ No _____
5	Prep. ____ RD ____ RF ____	NaOCl 2.5% ____ NaOCl 5.0% ____ Iodine 10% ____ CHX ____ EDTA 17% ____	Ledermix ___ Ca(OH)₂ ___ Antibiotics ___ Type _____	None ____ Glyde ____ Fileze ____ Hibiscrub ___	IRM ____ Band ____ Temp Cr. ____ Post ____	___ min	None ___ Loops ___ Scope ___	Yes _____ Intensity__/10 No _____	Yes _____ No _____	Yes _____ No _____

Existing crown retained: Yes ___, No ___, N/A ___
Final restoration base: None ___, IRM ___, GIC ___
Final restoration core placed: Yes ____, No ____

Core material – posterior teeth: amalgam ___, post+amal. ___, cast post & core ___
Restorative material in anterior teeth: composite _____, GIC _____

2

Canal measurement and preparation

Canal with notation[a]	Initial canal content	Apex Locator Zero Length	Working Length	Initial size [b]	MAF size	Taper of canal prep. [c]	File used	Patency Filing used	Root Filling Tech-nique [d]	Procedural Error	Canal Curvature	Level of difficulty
1st ____	Vital pulp ____ Blood ____ Exudate ____ Pus ____ Empty ____ Previous Tx ____	____mm Or not patent __	____ mm	# ____	# ____	.02___ .04___ .05___ .06___ .08___ .10___	SS ____ Hand NiTi ____ Rotary NiTi ____	Yes ___ No ___	CL ___ WL ___ UE ___ WV ___ CW ___	None ____ Ledge ____ # Inst. ____ Block ____ Perf. ____ Level: A/M/C	Curve? Y / N Position: A/M Plane: 1 / 2 No: 1 / 2 / 3	High ___ Average ___ Low ___
2nd ____	Vital pulp ____ Blood ____ Exudate ____ Pus ____ Empty ____ Previous Tx ____	____mm Or not patent __	____ mm	# ____	# ____	.02___ .04___ .05___ .06___ .08___ .10___	SS ____ Hand NiTi ____ Rotary NiTi ____	Yes ___ No ___	CL ___ WL ___ UE ___ WV ___ CW ___	None ____ Ledge ____ # Inst. ____ Block ____ Perf. ____ Level: A/M/C	Curve? Y / N Position: A/M Plane: 1 / 2 No: 1 / 2 / 3	High ___ Average ___ Low ___
3rd ____	Vital pulp ____ Blood ____ Exudate ____ Pus ____ Empty ____ Previous Tx ____	____mm Or not patent __	____ mm	# ____	# ____	.02___ .04___ .05___ .06___ .08___ .10___	SS ____ Hand NiTi ____ Rotary NiTi ____	Yes ___ No ___	CL ___ WL ___ UE ___ WV ___ CW ___	None ____ Ledge ____ # Inst. ____ Block ____ Perf. ____ Level: A/M/C	Curve? Y / N Position: A/M Plane: 1 / 2 No: 1 / 2 / 3	High ___ Average ___ Low ___
4th ____	Vital pulp ____ Blood ____ Exudate ____ Pus ____ Empty ____ Previous Tx ____	____mm Or not patent __	____ mm	# ____	# ____	.02___ .04___ .05___ .06___ .08___ .10___	SS ____ Hand NiTi ____ Rotary NiTi ____	Yes ___ No ___	CL ___ WL ___ UE ___ WV ___ CW ___	None ____ Ledge ____ # Inst. ____ Block ____ Perf. ____ Level: A/M/C	Curve? Y / N Position: A/M Plane: 1 / 2 No: 1 / 2 / 3	High ___ Average ___ Low ___

Apex Locator Brand: SybronEndo / RootZx / AFA
Other ____________

Failed to treat any canal? No ____, Yes ____ (if yes, which one _______)

[a] Identify canal as Single, Buccal, Lingual, Palatal, MB1, MB2, DB, DL, MB, ML
[b] The size of the 1st file that binds at the apex locator "zero" reading length prior to any apical preparation
[c] If varying taper instrument was used, select and mark the taper for apical (A), mid-root (M) and coronal (C) levels
[d] Root Filling Techniques: CL = cold lateral, WL = Finger spreader + Glass Bead Sterilizer, UE=U/S energization, WV = Schilder's warm vertical, CW=continuous wave

3

Additional Information specifically for re-treatment cases

Canal with notation[a]	Canal content	Foreign material present	Type of # instrument	Foreign material removed / bypassed	Existing perforation	Perf. repair material
1st ____	Un-instrumented ____ Instrumented but empty ____ Foreign material ____	$Ca(OH)_2$ ____ Gutta-percha ____ Paste ____ Thermafil ____ Silver point ____ # Instrument ____ Retro filling ____	Not Applicable K file ____ H file ____ NiTi file ____ Spiral filler ____	Removed ____ Bypassed ____ Neither ____	No ____ Yes ____ Coronal ____ Middle ____ Apical ____	Not applicable GIC ____ EBA ____ MTA ____ Other ________
2nd ____	Un-instrumented ____ Instrumented but empty ____ Foreign material ____	$Ca(OH)_2$ Gutta-percha ____ Paste ____ Thermafil ____ Silver point ____ # Instrument ____ Retro filling ____	Not Applicable K file ____ H file ____ NiTi file ____ Spiral filler ____	Removed ____ Bypassed ____ Neither ____	No ____ Yes ____ Coronal ____ Middle ____ Apical ____	Not applicable GIC ____ EBA ____ MTA ____ Other ________
3rd ____	Un-instrumented ____ Instrumented but empty ____ Foreign material ____	$Ca(OH)_2$ ____ Gutta-percha ____ Paste ____ Thermafil ____ Silver point ____ # Instrument ____ Retro filling ____	Not Applicable K file ____ H file ____ NiTi file ____ Spiral filler ____	Removed ____ Bypassed ____ Neither ____	No ____ Yes ____ Coronal ____ Middle ____ Apical ____	Not applicable GIC ____ EBA ____ MTA ____ Other ________
4th ____	Un-instrumented ____ Instrumented but empty ____ Foreign material ____	$Ca(OH)_2$ ____ Gutta-percha ____ Paste ____ Thermafil ____ Silver point ____ # Instrument ____ Retro filling ____	Not Applicable K file ____ H file ____ NiTi file ____ Spiral filler ____	Removed ____ Bypassed ____ Neither ____	No ____ Yes ____ Coronal ____ Middle ____ Apical ____	Not applicable GIC ____ EBA ____ MTA ____ Other ________

[a] Identify canal as Single, Buccal, Lingual, Palatal, MB1, MB2, DB, DL, MB, ML

4

Appendix VI

Endodontic treatment review form

Yuan-Ling Paula Ng

Endodontic treatment review form

A. Patient's name and Hospital no.

Has the tooth has been extracted? ____

If so, what was the reason_________ & time of extraction DD/MM/YY

Database number

B. Review Examination Tooth:

Review Date 1: ____/____/____ **Date of tx completion:** ___/___/___

Review Date 2: ____/____/____

Review Date 3: ____/____/____

Review Date 4: ____/____/____

Review Date 5: ____/____/____

Medical History: Nil / ___________________

Cast Restoration by: GDP / EDH

Cast Restoration placed _______**months after treatment**

Clinical: Pain ☐ Tender to Palpation ☐ Sinus ☐ Crown Fracture ☐ **0 = No**
1 = Yes

Swelling ☐ Tender to Percussion ☐ Attachment Loss ☐ **(record probing depth if >3mm)**

Mobility ☐ **0 = No mobility, 1 to 3 (< 1mm, 1 - 2mm, > 2mm), 4 = Vertical Mobility**

Final Restoration: Type ☐ **0 = Temporary Restoration** **1 = Tooth-coloured Restoration**
2 = Amalgam **3 = Cast Cusp-covered Restoration**

Post ☐ **0 = No, 1 = Yes**

Quality of Restoration: Open Margin ☐ Fracture ☐ Exposed Root Filling ☐

Occlusal Interference ☐ **0 = No, 1 = Yes**

1

Appendix VII

Radiographic assessment form

Radiographic assessment form

Patient ID: ☐ **Tooth ID:** ☐

Duration after completion of treatment: 1 yr ☐ 2 yr ☐ 3 yr ☐ 4yr ☐ 5yrs ☐ 6yrs ☐ 7yrs ☐

Tooth notation:

UR ☐ UL ☐ LR ☐ LL ☐

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐

Root notation*	Pre-op radiographic assessment	Content /quality	Final rad outcome ______months	Completion date	Recall 1 Date	Recall 2 Date	Recall 3 Date	Recall 4 Date
1st ☐	Intact PDL ☐ Widened PDL ☐ Pa lesion ☐ mm ☐	Content RF quality Extent	Unsuccessful ☐ Incomplete ☐ Uncertain ☐ Complete ☐	Pa size RF Sealer	Pa size Sealer	Pa size Sealer	Pa size Sealer	Pa size Sealer
2nd ☐	Intact PDL ☐ Widened PDL ☐ Pa lesion ☐ mm ☐	Content RF quality Extent	Unsuccessful ☐ Incomplete ☐ Uncertain ☐ Complete ☐	Pa size RF Sealer	Pa size Sealer	Pa size Sealer	Pa size Sealer	Pa size Sealer
3rd ☐	Intact PDL ☐ Widened PDL ☐ Pa lesion ☐ mm ☐	Content RF quality Extent	Unsuccessful ☐ Incomplete ☐ Uncertain ☐ Complete ☐	Pa size RF Sealer	Pa size Sealer	Pa size Sealer	Pa size Sealer	Pa size Sealer
4th ☐	Intact PDL ☐ Widened PDL ☐ Pa lesion ☐ mm ☐	Content RF quality Extent	Unsuccessful ☐ Incomplete ☐ Uncertain ☐ Complete ☐	Pa size RF Sealer	Pa size Sealer	Pa size Sealer	Pa size Sealer	Pa size Sealer

Appendix VIII

Published papers

1. **Ng Y-L**, Mann V, Rahbaran S, Lewsey J, Gulabivala K (2007) Outcome of primary root canal treatment: Systematic review of the literature – Part 1 (Effects of study characteristics). *International Endodontic Journal* **40**, 12–39.

2. **Ng Y-L**, Mann V, Rahbaran S, Lewsey J, Gulabivala K (2008a) Outcome of primary root canal treatment: Systematic review of the literature – Part 2 (Influence of clinical factors). *International Endodontic Journal* **41**, 6–31.

3. **Ng Y-L**, Mann V, Gulabivala K (2008b) Outcome of secondary root canal treatment: a systematic review of the literature. *International Endodontic Journal* **41**, 1026–46.

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REVIEW

Outcome of primary root canal treatment: systematic review of the literature – Part 1. Effects of study characteristics on probability of success

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Abstract

Ng Y-L, Mann V, Rahbaran S, Lewsey J, Gulabivala K. Outcome of primary root canal treatment: systematic review of the literature – Part 1. Effects of study characteristics on probability of success. *International Endodontic Journal*, **40**, 921–939, 2007.

Aims The aims of this study were (i) to conduct a comprehensive systematic review of the literature on the outcome of primary (initial or first time) root canal treatment; (ii) to investigate the influence of some study characteristics on the estimated pooled success rates.

Methodology Longitudinal clinical studies investigating outcome of primary root canal treatment, published up to the end of 2002, were identified electronically (MEDLINE and Cochrane database 1966–2002 December, week 4). Four journals (International Endodontic Journal, Journal of Endodontics, Oral Surgery Oral Medicine Oral Pathology Endodontics Radiology and Dental Traumatology & Endodontics), bibliographies of all relevant papers and review articles were hand-searched. Three reviewers (Y-LN, SR and KG) independently assessed, selected the studies based on specified inclusion criteria, and extracted the data onto a pre-designed proforma. The study inclusion criteria were: longitudinal clinical studies investigating root canal treatment outcome; only primary root canal treatment carried out on the teeth studied; sample size given; at least 6-month postoperative review; success based on clinical and/or radiographic criteria (strict, absence of apical radiolucency; loose, reduction in size of radiolucency); overall success rate given or could be calculated from the raw data. The findings by individual study were summarized and the pooled success rates by each potential influencing factor were calculated for this part of the study.

Results Of the 119 articles identified, 63 studies published from 1922 to 2002, fulfilling the inclusion criteria were selected for the review: six were randomized trials, seven were cohort studies and 48 were retrospective studies. The reported mean success rates ranged from 31% to 96% based on strict criteria or from 60% to 100% based on loose criteria, with substantial heterogeneity in the estimates of pooled success rates. Apart from the radiographic criteria of success, none of the other study characteristics could explain this heterogeneity. Twenty-four factors (patient and operative) had been investigated in various combinations in the studies reviewed. The influence of preoperative pulpal and periapical status of the teeth on treatment outcome were most frequently explored, but the influence of treatment technique was poorly investigated.

Conclusions The estimated weighted pooled success rates of treatments completed at least 1 year prior to review, ranged between 68% and 85% when strict criteria were used. The reported success rates had not improved over the last four (or five) decades. The quality of evidence for treatment factors affecting primary root canal treatment outcome is sub-optimal; there was substantial variation in the study–designs. It

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would be desirable to standardize aspects of study-design, data recording and presentation format of outcome data in the much needed future outcome studies.

Keywords: outcome, root canal treatment, success, systematic review.

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Introduction

There has been a surge of interest in formulating clinical guidelines for optimal treatment of diseases based on properly conceived and executed research. The gold standard for informing clinical practice is putatively the randomized controlled trial (RCT); however, neither medical nor dental practice has been generally well supported by such evidence. Sackett *et al.* (1996) now famous definition, 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients', not only embraces the notion of grades of evidence but also recognizes that optimal levels of evidence may not be available for all situations. There is therefore a need to synthesize an objective over-view based on *available* evidence. Depending upon the quality and quantity of the data, systematic reviews can be of several different kinds: traditional reviews; meta-analysis leading to an estimate of effect size; best evidence synthesis; and the hypothetico-deductive approach, in which the effort is directed at evaluating the evidence for and against a given theory, in an attempt to solve the problem of why contradictory results appear, rather than simply averaging often incompatible data (Eysenck 1994).

For the outcome of endodontic treatment, there are eight published systematic reviews, which have used different approaches in synthesis of information from the literature. Basmadjian-Charles *et al.* (2002) and Paik *et al.* (2004) used a systematic approach for literature search but a traditional approach for evaluating the variables impacting on the success and failure of the root canal retreatment. Two reviews (Hepworth & Friedman 1997, Peterson & Gutmann 2001) calculated the weighted-average success rates by each factor under investigation. Neiderman & Theodosopoulou (2003) estimated the number needed to treat when comparing two types of treatments. Three reviews (Lewsey *et al.* 2001, Kojima *et al.* 2004, Sathorn *et al.* 2005) estimated the size of effect of individual factors which included presence of preoperative pulpal and periapical status, apical extent of root filling & number of treatment visits, using meta-analysis. Except for Lewsey *et al.* (2001), none have investigated the influence of study characteristics such as radiographic criteria for determination of treatment outcome and year of publication, on the data heterogeneity.

In the absence of sufficient gold standard level data, there is a need to synthesize 'sub-standard' data but there is a lack of formal guidelines to achieve this. In the absence of such guidelines, the authors proposed the use of a process of 'triangulation' of different analytical approaches as a sensible strategy. The purpose of this systematic review and synthesis was to: (i) identify the probable dominant factors influencing outcome; (ii) help prioritize the questions that need to be addressed; (iii) inform the design and data collection protocol for future RCTs. The outcome of this analysis will be presented in two parts.

The aim of the first part of this paper is to present the estimated pooled success rates of primary root canal treatment by aspects of study characteristics: decade of publication, study-specific criteria for success, unit of outcome measure, duration after treatment, geographical location of study and qualification of the operator.

Materials and methods

Literature search

Longitudinal clinical studies investigating the outcome of primary root canal treatment that were published up to the end of 2002 were identified electronically (MEDLINE database 1966 2002 December, week 4) using six keywords (root canal treatment, root canal therapy, endodontic treatment, endodontics, treatment outcome and success) and eight strategies (1 AND 5, 1 AND 6, 2 AND 5, 2 AND 6, 3 AND 5, 3 AND 6, 4 AND 5 and 4 AND 6). A Cochrane Library search was also conducted. PubMed was independently searched using the 'related articles' feature. Four journals (International Endodontic Journal, Journal of Endodontics, Oral Surgery Oral Medicine Oral Pathology Endodontics Radiology and Dental Traumatology & Endodontics) and bibliographies of all relevant papers and review articles were hand-searched. Unpublished studies were identified by searching abstracts and conference proceedings. Personal contacts were also used to identify ongoing or unpublished studies. Full articles were obtained for all relevant titles identified through either electronic or other search methods.

Study selection, quality assessment and data extraction

Three reviewers (Y-LN, SR and KG) independently assessed and selected the studies based on the following inclusion criteria:
1. Clinical study on primary root canal treatment.
2. Stratified analysis of primary root canal treatment available, if root canal re-treatment cases had been included.
3. Sample size given.
4. At least 6-month postoperative review.
5. Success based on clinical and/or radiographic (strict, absence of apical radiolucency; loose, reduction in size of radiolucency) criteria.
6. Overall success rate given or could be calculated from the raw data.
7. Presentations in English, German, Chinese and Japanese languages were accepted.

Disagreements on study inclusion were resolved by discussion. The reasons for study rejection at this or subsequent stages were recorded.

Data were extracted by all three reviewers independently using custom-designed data collection forms. The data collection form was piloted on several papers and modified for optimal utility before final use. The data extracted could be classified into six groups: success rates, study characteristics, demographic data of patients, pre-, intra- and postoperative factors. Any disagreement was discussed and data were excluded if agreement could not be reached.

Estimation of pooled success rates

STATA version 9.2 statistical software (StataCorp, College Station, TX, USA) was used to perform all statistical analyses. Un-weighted pooled success rate by each factor was calculated by dividing the total number of successful units with the total number of units within the respective category (according to Hepworth & Friedman 1997). In addition, the weighted pooled success rates were estimated using random effects meta-analysis with DerSimonian and Laird's methods (DerSimonian & Laird 1986). Statistical heterogeneity amongst the studies was assessed by Cochran's (Q) test (Cochran 1954).

Meta-regression models (Thompson & Higgins 2002) were used to explore the potential sources of statistical heterogeneity and to assess the effect of factors on estimating the pooled success rate. Factors related with study characteristics considered in the meta-regression analyses as covariates (and their sub-categories) were: decade of publication, study specific criteria (radiographic, combined radiographical & clinical) for success, unit of outcome measure (tooth and root), duration after treatment when assessing success ('at least 4 years' or '<4 years'), geographical location of the study (North American, Scandinavian and other countries), qualification of the operator (undergraduate students, postgraduate students, general dental practitioners (GDP), specialist or mixed group). If either the estimated proportion of total variation because of heterogeneity across studies (I^2) or the estimated between-study variance (τ^2) from the meta-regression model without covariate in the model was reduced substantially (>10%) when a covariate was included into the model, the respective covariate was considered to be a potential source of heterogeneity.

Results

A total of 119 papers were identified in the initial search, 51 articles were excluded for the reasons given in Table 1. Some papers presented different parts of the same study, so their data were combined for analyses in this review: (i) Heling & Tamshe (1970, 1971); (ii) Barbakow *et al.* (1980a,b, 1981); (iii) Morse *et al.* (1983a,b,c); (iv) Ørstavik *et al.* (1987) & Eriksen *et al.* (1988). Conversely, Kerekes (1978) presented two separate data sets in their paper, and were therefore considered as two separate studies in this review. As a result, 63 studies fulfilling the inclusion criteria were selected for this review. The year of publication of the selected studies ranged from 1922 to 2002 with the highest number of studies published in the 1980s ($n = 16$) (Table 2).

Each reviewer had entered 174 data points per selected study and the initial agreements amongst the three reviewers were moderate ($\kappa = 0.57$ 0.61). As per protocol, following discussion about any disagreements, there was 100% concurrence on used data.

Methodological characteristics of included studies

Of the 63 studies included in this review, six were RCTs (Table 2). Others were cohort studies ($n = 8$) or retrospective observational studies ($n = 49$). Although

Table 1 Reasons for exclusion of the 51 articles

Article	Inclusion criteria (1–6) not fulfilled or other reasons for exclusion
Grove (1921)	[1]Clinical study for primary root canal treatment
Hinman (1921)	[3]Sample size given
	[6]Overall success rate given or could be calculated
Grove (1923)	[1]Clinical study for primary root canal treatment
Coolidge (1926)	[6]Overall success rate given or could be calculated
Rhein *et al.* (1926)	[4]At least 6-month postoperative review
Puterbaugh (1926)	[3]Sample size given
	[6]Overall success rate given or could be calculated
Hall (1928)	[1]Clinical study for primary root canal treatment
Appleton (1932)	[4]At least 6-month postoperative review
Buchbinder (1936)	[2]Stratified analysis available
Macphee (1936)	[6]Overall success rate given or could be calculated
Strindberg (1956)	[2]Stratified analysis of one RCT available
Frostell (1963)	[2]Stratified analysis of one RCT available
Nichols (1963)	[1]Clinical study for primary root canal treatment
Grossman *et al.* (1964)	[2]Stratified analysis of one RCT available
Engström *et al.* (1964)	[2]Stratified analysis of one RCT available
Ingle *et al.* (1965)	[2]Stratified analysis of one RCT available
Curson (1966)	[1]Clinical study for primary root canal treatment
Oliet & Sorin (1969)	[5]Success based on clinical and/or radiographic criteria
Storms (1969)	[2]Stratified analysis of one RCT available
Ratliff (1973)	[5]Success based on clinical and/or radiographic criteria
Cvek *et al.* (1976)	[2]Stratified analysis of one RCT available
Adenubi (1978)	Same data set as Adenubi & Rule (1976)
Taintor *et al.* (1978)	[1]Clinical study for primary root canal treatment
Vernieks & Messer (1978)	[2]Stratified analysis of one RCT available
Kerekes & Tronstad (1979)	[2]Stratified analysis of one RCT available
Markitziu & Heling (1981)	[1]Clinical study for primary root canal treatment
Hession (1981)	[2]Stratified analysis of one RCT available
Thoden van Velzen *et al.* (1981)	Same data set as Kerekes & Tronstad (1979)
Ashkenaz (1984)	[5]Success based on clinical and/or radiographic criteria
Seto *et al.* (1985)	[5]Success based on clinical and/or radiographic criteria
Ørstavik *et al.* (1986)	[6]Overall success rate given or could be calculated
Teo *et al.* (1986)	[2]Stratified analysis of one RCT available
Kullendorff *et al.* (1988)	[1]Clinical study for primary root canal treatment
Molven & Halse (1988)	[2]Stratified analysis of one RCT available
	Same data set as Halse & Molven (1987)
Augsburger & Peters (1990)	[4]At least 6-month postoperative review
	[5]Success based on clinical and/or radiographic criteria
Stabholz (1990)	[1]Clinical study for primary root canal treatment
Wong *et al.* (1992)	[5]Success based on clinical and/or radiographic criteria
Ørstavik & Hörsted-Bindslev (1993)	[6]Overall success rate given or could be calculated
Gutknecht *et al.* (1996)	[4]At least 6-month postoperative review
Friedman (1997)	[1]Clinical study for primary root canal treatment
Ricucci & Langeland (1997)	[1]Clinical study for primary root canal treatment
Weine & Buchanan (1997)	[1]Clinical study for primary root canal treatment
Shi *et al.* (1997)	[5]Success based on clinical and/or radiographic criteria
Weiger *et al.* (1998)	[1]Clinical study for primary root canal treatment
Caplan & White (2001)	[5]Success based on clinical and/or radiographic criteria
Oliver & Abbott (2001)	[1]Clinical study for primary root canal treatment
Waltimo *et al.* (2001)	[6]Overall success rate given or could be calculated
Lazarski *et al.* (2001)	[5]Success based on clinical and/or radiographic criteria
Lynch *et al.* (2002)	[5]Success based on clinical and/or radiographic criteria
Caplan *et al.* (2002)	[5]Success based on clinical and/or radiographic criteria
Murakami *et al.* (2002)	[4]At least 6-month postoperative review

nine studies (Grahnén & Hansen 1961, Storms 1969, Selden 1974, Heling & Kischinovsky 1979, Pekruhn 1986, Sjögren *et al.* 1990, Friedman *et al.* 1995, Chugal *et al.* 2001, Hoskinson *et al.* 2002) had included previously root-filled teeth in their sample, they had provided stratified analysis for primary treatment.

The recall rates (percentage of patients attending for follow-up after treatment) were reported by 39 studies and ranged from 11% to 100% with a median of 52.7%. Either root (27 studies) or tooth (36 studies) was used as the unit of outcome measure. The sample sizes ranged from 22 to 2921 teeth or 38 to 2921 roots; some studies only included single-rooted teeth, hence the number of teeth and roots were the same.

The treatment outcome was determined by radiographic examination alone (27 studies) or in combination with clinical findings (36 studies) (Table 2). Different radiographic criteria of success have been used and these were divided into: 'strict' (complete resolution of peri-apical lesion at recall) or 'loose' (reduction in size of existing peri-apical lesion at recall). For the radiographic assessment of the outcome of treatment, only 19 studies (Table 2) employed at least two observers to carry out the assessment. Observer(s) were calibrated prior to evaluation of radiographs in eight studies and intra- or inter-observer reliability tests were carried out in nine studies (Table 2).

Different studies have evaluated the influence of a range of different clinical prognostic factors on outcome but the combinations of factors reported vary (Table 3). The statistical methods used for analysing the association between potential influencing factors and treatment outcome were the chi-square test (31 studies), relative incidence distribution (two studies), logistical regression models (three studies), ANOVA (two studies), survival analysis (one study) and logistic regression models using generalized estimating equations (one study) (Table 2). Twenty-three studies did not analyse the data statistically or did not present such information.

Success rates by study characteristics

Outcome measure used

The reported success rates of root canal treatment ranged from 31% to 96% based on strict criteria and from 60% to 100% based on loose criteria. The weighted pooled success rates from studies using 'strict' criteria (data available from 40 studies) were about 10% lower than those from studies using 'loose' criteria (data available from 38 studies) regardless of examination method used (Table 4). Some studies ($n = 14$) presented the success rates stratified by both strict and loose criteria.

After combining the data from the two examination methods, the pooled success rates estimated by meta-analyses were 74.7% (95% CI: 69.8–79.5%) from 40 studies using strict radiographic criteria and 85.2% (95% CI: 82.2–88.3%) from 36 studies using loose radiographic criteria. The estimated success rates by individual studies as well as the weighted pooled success rates by the two radiographic criteria are presented as Forrest plots in Figs 1 and 2. Meta-regression analyses showed the reported success rates based on strict radiographic criteria were 10.5% (4.4–16.7%, $P = 0.001$) lower than the success rates based on loose radiographic criteria. The radiographic criteria were also found to be responsible for part of the statistical heterogeneity, therefore the estimated success rates by individual factors were calculated separately for data based on the use of strict or loose criteria.

Duration after treatment completion

Most studies did not standardize the duration after treatment completion when the outcomes were reviewed, which ranged from 6 months to 30 years. Only 15 studies (Table 2) followed-up all the cases for at least 4 years. Attempts to pool data on success rates by different follow-up durations are confounded by the relatively small study numbers in some groups and may have produced distorted results. When strict criteria were used, the pooled success rates increased with longer follow-ups; the substantial increases were between 6 and 12 months and between 24 and 36 months after treatment (Table 4). However, there was no obvious trend in success rate by duration after treatment when loose criteria were used.

Year of publication

The pooled success rates based on 'loose' outcome criteria for each decade since the 1920s appeared to be similar with the highest pooled success rate at 88.2% during the 1980s (Table 4). However, the pooled success rates based on 'strict' outcome criteria for studies published during 1960s (79.7%) and 1970s (79.0%) were the highest. More importantly, the expected trend of progressively increasing success rates over the last century was clearly not in evidence.

Geographical location of study

About one-third of the studies were carried out in the USA or Canada (24 studies) and the rest were carried

Table 2 Study characteristics

Author (year)	Geographic location of study	[a]Study–design	Recall rate (%)	≥4 year follow-up after treatment	[b]Unit of measure	Sample size	[c]Assessment of success	[d]Radiographic criteria of success	≥2 radiographic observers	Calibration	Reliability test	[e]Statistical analysis
Blayney (1922)	USA	R	28		T	104	C&R	L				
Auerbach (1938)	USA	R	22		T	211	C&R	L				
Buchbinder (1941)	USA	R	–		Ro	245	Ra	S				
Morse & Yates (1941)	USA	R	–		T	265	Ra	L				
Castagnola & Orlay (1952)	Scandinavia	R	68		T	1000	C&R	S				
Grahnén & Hansen (1961)	Scandinavia	R	44	✔	Ro	1277	C&R	S	✔			
Seltzer *et al.* (1963)	USA	C	–		Ro	2921	Ra	L				
Zeldow & Ingle (1963)	USA	C	–		T	42	C&R	L				
Bender *et al.* (1964)	USA	R	30		Ro	706	Ra	L	✔			
Engström & Lundberg (1965)	Scandinavia	R	74		Ro	181	Ra	S				
Harty *et al.* (1970)	UK	R	60		Ro	1139	C&R	S				χ^2
Heling & Tamshe (1970, 1971)	Israel	R	27		T	213	C&R	S				
Cvek (1972)	Scandinavia	R	–		Ro	55	Ra	S				ANOVA
Selden (1974)	USA	R	11		T	556	Ra	L				χ^2
Werts (1975)	USA	R	23	✔	T	47	C&R	S				
Adenubi & Rule (1976)	UK	R	–		Ro	870	C&R	S				χ^2
Heling & Shapira (1978)	Israel	R	17		T	118	C&R	S				
Jokinen *et al.* (1978)	Scandinavia	R	45		Ro	2459	C&R	S	✔			χ^2
Kerekes (1978)	Scandinavia	R	–		Ro	379	Ra	S	✔			χ^2
Kerekes (1978)	Scandinavia	R	–		Ro	188	Ra	S	✔			χ^2
Soltanoff (1978)	USA	R	–		T	266	Ra	L				
Heling & Kischinovsky (1979)	Switzerland	R	13		Ro	202	C&R	L				χ^2
Barbakow *et al.* (1980a,b, 1981)	South Africa	R	60		T	335	C&R	L				χ^2
Cvek *et al.* (1982)	Scandinavia	R	83	✔	Ro	45	Ra	S				χ^2
Nelson (1982)	UK	R	–		T	299	C&R	L				χ^2
Boggia (1983)	UK	R	–		T	52	Ra	S				
Klevant & Eggink (1983)	Holland	R	76		T	319	Ra	S				χ^2
Morse *et al.* (1983a,b,c)	USA	R	–		Ro	458	C&R	L				χ^2
Oliet (1983)	USA	C	–		T	338	C&R	L				χ^2
Swartz *et al.* (1983)	USA	R	–		Ro	1770	C&R	L				χ^2
Pekruhn (1986)	Saudi Arabia	R	81		T	925	C&R	S				χ^2
Byström *et al.* (1987)	USA	C	56		Ro	79	Ra	S	✔			χ^2
Halse & Molven (1987)	Scandinavia	R	63	✔	Ro	551	Ra	S				χ^2
Matsumoto *et al.* (1987)	Japan	R	38		T	85	C&R	L				χ^2
Ørstavik *et al.* (1987) & Eriksen *et al.* (1988)	Scandinavia	RCT	36	✔	Ro	289	Ra	L		✔	✔	RIDIT
Safavi *et al.* (1987)	USA	R	–		T	464	C&R	S	✔	✔	✔	χ^2
Akerblom & Hasselgren (1988)	Scandinavia	R	73		Ro	64	C&R	S	✔			
Shah (1988)	India	C	70		T	65	C&R	L				
Sjögren *et al.* (1990)	Scandinavia	R	46	✔	Ro	573	Ra	S	✔	✔	✔	LR
Murphy *et al.* (1991)	USA	R	–		T	89	Ra	S				
Cvek (1992)	Scandinavia	R	76	✔	Ro	610	Ra	S				χ^2
Reid *et al.* (1992)	Australia	RCT	44	✔	Ro	74	C&R	S	✔			χ^2
Jurcak *et al.* (1993)	USA	R	58		T	102	C&R	L	✔			
Smith *et al.* (1993)	UK	R	54	✔	T	821	C&R	L				χ^2
Peak (1994)	UK	R	–		T	136	C&R	S			✔	χ^2
Friedman *et al.* (1995)	Canada	C	78		T	250	C&R	S				χ^2
Çalişken & Şen (1996)	Turkey	R	–		T	172	C&R	S				
Østavik (1996)	Scandinavia	C	81	✔	Ro	599	Ra	L		✔	✔	RIDIT
Peretz *et al.* (1997)	Israel	R	–		T	28	C&R	S				χ^2
Sjögren *et al.* (1997)	Scandinavia	C	96	✔	Ro	53	Ra	S	✔	✔		
Lilly *et al.* (1998)	USA	R	–		T	22	C&R	S	✔			
Trope *et al.* (1999)	USA	RCT	–		T	102	Ra	S	✔	✔	✔	χ^2
Ricucci *et al.* (2000)	Italy	R	–		T	110	Ra	S	✔			χ^2
Weiger *et al.* (2000)	Germany	RCT	92		T	67	C&R	S	✔			LR
Chugal *et al.* (2001)	USA	R	75	✔	R	322	Ra	S	✔			LR
Deutsch *et al.* (2001)	USA	R	42		T	153	C&R	L				χ^2
Heling *et al.* (2001)	Israel	R	–		T	319	Ra	L				ANOVA
Peak *et al.* (2001)	UK	R	–	✔	T	406	C&R	L			✔	
Pettiette *et al.* (2001)	USA	RCT	66		T	40	Ra	L				χ^2
Benenati & Khajotia (2002)	USA	R	29		T	894	Ra	S				χ^2
Cheung (2002)	Hong Kong	R	28	✔	T	282	C&R	S				Survival
Hoskinson *et al.* (2002)	UK	R	42	✔	Ro	413	C&R	S	✔	✔	✔	GEE
Peters & Wesselink (2002)	Holland	RCT	100		Ro	38	C&R	S	✔	✔	✔	χ^2

[a]R, retrospective study; C, prospective cohort study; RCT, randomized controlled trial.
[b]T, teeth; Ro, root (unit of measure was recorded as 'root' for those studies which has only included single rooted teeth in their sample).
[c]C&R, combined clinical and radiographic examination; Ra, radiographic examination only.
[d]S, strict criteria; L, loose criteria.
[e]LR, single level logistic regression; GEE, generalized estimating equations; χ^2, chi-squared test; RIDIT, relative incidence distribution; ANOVA, analysis of variance; Survival, survival analysis.

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Table 3 Clinical prognostic factors included in studies

Author (year)	Gender	Age	Health	Tooth type	Pulpal status	Periapical status	Lesion size	Rubber dam	Obstruction	Apical size	Canal taper	Irrigant	Medicament	Culture test	RF material technique	Sealer	RF extent	Quality of RF	Acute flare up	Apical disturbance	Visits of treatment	Restoration	Abutment
Blayney (1922)					✔	✔		✔				✔											
Auerbach (1938)					✔	✔						✔											
Buchbinder (1941)					✔	✔		✔				✔	✔	✔							✔		
Morse & Yates (1941)					✔	✔		✔				✔		✔							✔		
Castagnola & Orlay (1952)					✔	✔		✔													✔		
Grahnén & Hansen (1961)					✔	✔						✔			✔		✔				✔		
Seltzer *et al.* (1963)		✔			✔	✔								✔	✔		✔						
Zeldow & Ingle (1963)								✔				✔		✔	✔						✔		
Bender *et al.* (1964)					✔	✔								✔	✔		✔				✔		
Engström & Lundberg (1965)					✔								✔	✔							✔		
Harty *et al.* (1970)		✔						✔				✔					✔	✔		✔	✔		
Heling & Tamshe (1970, 1971)					✔	✔		✔				✔	✔			✔	✔						
Cvek (1972)					✔	✔		✔				✔		✔							✔		
Selden (1974)					✔	✔	✔																
Werts (1975)					✔	✔																	
Adenubi & Rule (1976)	✔	✔		✔	✔	✔						✔	✔		✔	✔	✔	✔		✔	✔		
Heling & Shapira (1978)					✔	✔		✔					✔	✔	✔	✔	✔				✔	✔	
Jokinen *et al.* (1978)	✔	✔		✔	✔	✔							✔		✔		✔				✔		✔
Kerekes (1978)				✔											✔		✔	✔					
Kerekes (1978)				✔				✔							✔		✔	✔					
Soltanoff (1978)												✔			✔		✔				✔		
Heling & Kischinovsky (1979)					✔	✔		✔				✔	✔		✔	✔	✔						
Barbakow *et al.* (1980a,b, 1981)		✔		✔	✔	✔		✔					✔		✔	✔	✔				✔		
Cvek *et al.* (1982)					✔	✔		✔	✔			✔			✔								
Nelson (1982)		✔			✔	✔										✔	✔	✔		✔			
Boggia (1983)					✔	✔										✔	✔			✔	✔		
Klevant & Eggink (1983)								✔				✔	✔			✔	✔						
Morse *et al.* (1983a,b,c)					✔	✔						✔	✔		✔		✔				✔		
Oliet (1983)	✔	✔			✔	✔						✔			✔	✔	✔				✔		
Swartz *et al.* (1983)	✔	✔		✔		✔									✔		✔					✔	
Pekruhn (1986)					✔	✔		✔				✔				✔					✔		
Byström *et al.* (1987)					✔	✔		✔						✔	✔		✔				✔		
Halse & Molven (1987)					✔	✔									✔		✔						
Matsumoto *et al.* (1987)					✔	✔	✔	✔					✔	✔			✔				✔		✔
Ørstavik *et al.* (1987) & Eriksen *et al.* (1988)					✔	✔						✔											
Safavi *et al.* (1987)					✔	✔						✔		✔	✔	✔					✔	✔	
Akerblom & Hasselgren (1988)					✔	✔	✔	✔	✔			✔	✔		✔						✔		
Shah (1988)					✔	✔		✔							✔	✔					✔		
Sjögren *et al.* (1990)				✔	✔	✔	✔	✔				✔		✔	✔		✔	✔			✔		
Murphy *et al.* (1991)					✔	✔																	
Cvek (1992)					✔	✔									✔		✔				✔		
Reid *et al.* (1992)								✔					✔		✔	✔					✔		
Jurcak *et al.* (1993)				✔											✔						✔		
Smith *et al.* (1993)	✔	✔			✔	✔		✔			✔				✔	✔	✔				✔		
Peak (1994)				✔	✔	✔									✔		✔						
Friedman *et al.* (1995)					✔	✔						✔	✔		✔	✔							
Çalişken & Şen (1996)			✔		✔	✔	✔	✔				✔	✔		✔	✔				✔	✔		
Østavik (1996)					✔	✔		✔				✔											
Peretz *et al.* (1997)		✔			✔	✔																	
Sjögren *et al.* (1997)					✔	✔		✔				✔		✔	✔						✔		
Lilly *et al.* (1998)			✔		✔	✔									✔	✔						✔	
Trope *et al.* (1999)			✔					✔				✔	✔		✔	✔					✔		
Ricucci *et al.* (2000)								✔				✔			✔							✔	
Weiger *et al.* (2000)					✔	✔		✔				✔	✔		✔	✔					✔		
Chugal *et al.* (2001)					✔																		
Deutsch *et al.* (2001)					✔			✔				✔			✔	✔					✔		
Heling *et al.* (2001)					✔	✔						✔				✔	✔	✔				✔	
Peak *et al.* (2001)				✔	✔	✔									✔		✔						
Pettiette *et al.* (2001)					✔	✔																	
Benenati & Khajotia (2002)	✔	✔		✔												✔							
Cheung (2002)	✔	✔		✔	✔	✔		✔					✔		✔	✔					✔		
Hoskinson *et al.* (2002)	✔	✔		✔	✔	✔	✔	✔		✔	✔	✔	✔			✔	✔					✔	
Peters & Wesselink (2002)			✔		✔	✔		✔				✔	✔	✔	✔	✔					✔	✔	
Total	8	13	4	13	51	49	6	33	2	1	2	32	20	14	38	25	29	7	0	5	35	8	2

RF, root filling.

Table 4 Estimated success rates by study characteristics

Factor/categories	[a]No. studies identified	Strict radiographic criteria: No. studies	No. units	Estimated pooled success rates: [c]Un-weighted (%)	[d]Weighted (%)	Loose radiographic criteria: No. studies	No. units	Estimated pooled success rates: [c]Un-weighted (%)	[d]Weighted (%)
Outcome measure used									
Radiographic	27	17	4745	74.4	74.1 (66.9–81.3)	14 (13)[b]	7177	83.4	84.1 (79.0–89.3)
Clinical + radiographic	36	23	10799	72.8	75.0 (68.4–81.7)	24 (23)[b]	10430	82.0	85.8 (81.8–89.9)
Duration after treatment (months)									
6	4	2	1120	17.3	29.6 (14.2–73.3)	2	4633	89.1	89.1 (78.8–99.5)
12	9	5	2080	68.6	67.7 (39.0–96.4)	4	798	76.7	69.5 (52.3–86.6)
24	6	3	2328	75.8	67.3 (43.8–90.9)	3	1103	82.7	82.5 (75.2–89.8)
36	5	2	941	80.4	80.6 (78.0–83.1)	3	254	69.3	66.6 (36.1–95.9)
48	6	5	2931	84.5	83.8 (79.3–88.3)	2	301	93.5	61.7 (25.0–96.0)
>48	9	8	1162	86.8	85.4 (80.3–90.6)	1	821	84.3	84.3 (81.8–86.8)
Year of publication									
Before 1960	5	2	1245	68.2	68.2 (65.6–70.8)	4	1580	82.2	84.2 (72.2–96.1)
1960s	5	2	1458	81.3	79.7 (74.0–85.4)	3	3669	80.4	80.4 (79.2–81.7)
1970s	12	9	5468	69.8	79.0 (66.7–91.3)	6 (5)[b]	4400	77.0	84.0 (71.3–96.6)
1980s	16	9	2834	77.8	74.8 (62.5–87.0)	10 (9)[b]	3770	89.7	88.2 (85.0–91.4)
1990s	14	10	2007	83.9	76.9 (69.7–84.1)	8	2271	83.3	85.5 (80.2–90.9)
2000s	11	8	2532	65.2	68.0 (60.5–75.4)	7	1917	85.2	85.1 (78.0–92.3)
Geographic location of study									
USA or Canada	24	9	2412	67.5	74.1 (64.9–83.2)	20 (19)[b]	9393	86.5	88.1 (84.9–91.2)
Scandinavian country	15	12	6435	71.5	80.5 (71.1–89.8)	3 (2)[b]	3347	70.4	70.3 (61.3–79.2)
Other country	24	19	6697	76.9	71.2 (64.4–78.1)	15	4867	83.4	84.5 (80.4–88.5)
Qualification of operators									
Undergraduate students	21	14	8306	68.4	74.8 (67.0–82.7)	11 (10)[b]	7808	79.9	83.3 (75.8–90.9)
GDP	7	6	1353	64.4	65.7 (56.3–75.1)	5	1228	85.5	86.2 (82.9–89.5)
Postgraduate students	4	4	1336	82.9	77.2 (64.5–89.8)	2	959	93.1	93.1 (91.5–94.7)
Specialist	23	11	3288	87.6	84.8 (80.1–89.4)	17 (16)[b]	6368	84.7	87.6 (83.9–91.3)

GDP, general dental practitioners.
[a]Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported success rates based on both criteria.
[b]Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% rates by the respective factor under investigation have been excluded.
[c]Un-weighted pooled success rates were estimated based on the Hepworth & Friedman (1997)'s approach.
[d]Weighted pooled success rates were estimated using random effects meta-analysis (where there was only one study, its reported success rate and confident intervals were presented).

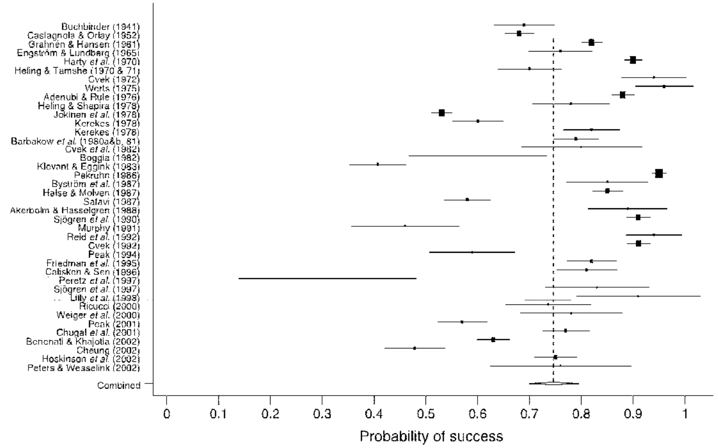

Figure 1 Probability of success based on strict radiographic criteria.

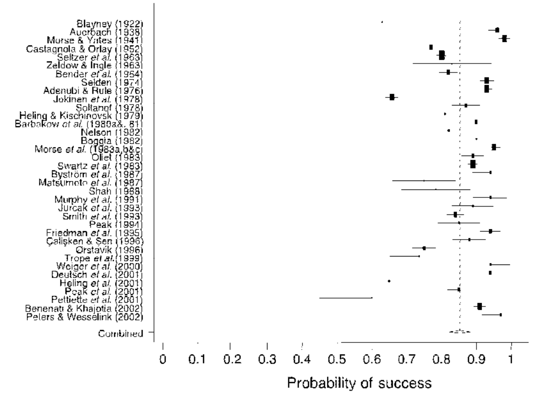

Figure 2 Probability of success based on loose radiographic criteria.

out in Scandinavian (15 studies, Sweden/Norway) or other countries (24 studies) including: UK (eight studies), Israel (four studies), Holland (two studies), Switzerland (one study), Australia (one study), Germany (one study), Hong Kong (one study), India (one study), Italy (one study), Japan (one study), Saudi

Arabia (one study), South Africa (one study) and Turkey (one study) (Table 2). The studies performed in the North American countries reported the treatment outcome data more frequently based on loose radiographic criteria than on strict criteria. In contrast, most of the outcome data from the Scandinavian countries were based on strict rather than loose criteria. Based on the loose criteria, the pooled estimate of success rate of treatment carried out in Scandinavian countries (70.3%) was much lower than for those in North American (88.1%) or other (84.5%) countries; however, the pooled estimate for the Scandinavian countries, only consisted of two studies. In stark contrast, the pooled estimate of success rate from outcome data based on strict criteria from the Scandinavian countries (80.5%) was the highest (Table 4).

Qualification of operators (undergraduate, postgraduate, GDP and specialist)

Only two studies compared the outcome of root canal treatment by qualification of operators. Ingle *et al.* (1965) (a study excluded from this review: Table 1), found no significant difference in success rates of treatment carried out by undergraduates or private practitioners, in agreement with Cheung (2002) who reported the qualification and experience of operator had no influence on treatment outcome.

The majority of the reviewed studies classified operator qualification as: undergraduate students (21 studies), GDP (seven studies), postgraduate students (four studies) or specialists (23 studies). In five studies, treatment was carried out by a mixed group of operators and three studies did not provide this information. From the results, treatment carried out by postgraduate students and specialists had the highest weighted pooled estimate of success, regardless of strict or loose criteria (Table 4).

Source of heterogeneity

As the radiographic criteria for success have already been shown to have a significant effect on the pooled success rates, further meta-regression analyses were therefore carried out, separately on success rates based on strict or loose criteria, to explore which of the other study characteristics were potentially responsible for the statistical heterogeneity. None had significant effects on the success rates reported by the studies or could account for the heterogeneity (Table 5) in estimating the pooled success rate of primary root canal treatment.

Table 5 Results of meta-regression analysis to account for the source of heterogeneity

Covariate included	Strict I^2	Strict τ^2	Loose I^2	Loose τ^2
No. covariate included	0.985	0.0247	0.973	0.0085
Year of publication (before 1970s, 1970–1989, 1990–2002)	0.983	0.0265	0.971	0.0098
Geographical location of study (USA, Scandinavian or other countries)	0.984	0.0244	0.952	0.0069
Unit of measure (root or tooth)	0.984	0.0253	0.961	0.0081
Qualification of operator (specialist, postgraduate, undergraduate, GDP or mixed group)	0.979	0.0209	0.974	0.0073
Criteria for success (radiographic vs. combined radiographic & clinical)	0.986	0.0254	0.974	0.0088
Duration after treatment (at least 4 years or shorter)	0.985	0.0228	0.973	0.0085
Recall rate	0.986	0.0218	0.975	0.0117

GDP, general dental practitioners; I^2, proportion of total variation due to heterogeneity across studies; τ^2, estimate of between-study variance (if the I^2 and τ^2 values were reduced by 10% after including a covariate in the regression model as compared with the values estimated without any covariates entered, the respective covariate was considered to be a potential source of heterogeneity).

Discussion

Most of the selected studies were prospective cohort or retrospective studies, therefore the levels of evidence provided by them are grade B (levels 2 or 3) based on the criteria given by the Oxford centre for evidence-based medicine (Phillips *et al.* 1998 http://www.cebm.net/index.aspx?0=1025). There were only six randomized trials investigating different aspects of root canal treatment procedures on outcomes, including the effects of scalers (AH26 [DeTrey AG, Zurich, Switzerland]; Procosol [Star Dental, Conshohocken, PA, USA], Kloropercha) (Ørstavik *et al.* 1987); root filling materials (Hydron® [Hydron Technologies, Pompano Beach, FL, USA], gutta-percha with AH26® sealer) (Reid *et al.* 1992); single-visit versus multiple-visit root canal treatment (Trope *et al.* 1999, Weiger *et al.* 2000, Peters & Wesselink 2002); use of $Ca(OH)_2$ dressing versus no medicament in multiple-visit treatment (Trope *et al.* 1999); and the use of stainless steel versus nickel titanium hand files (Pettiette *et al.* 2001).

The Cochrane Oral Health group's current guidelines for a systematic review states that 'the scope of the review is to include all RCTs, where RCTs are inappropriate, rather than unavailable, other levels of evidence may be considered' (http://www.ohg.cochrane.org/forms/writing_review.pdf September 2006). However, the authors decided that the numerous observational studies, whilst not having the feature of randomization or control groups, represented useful and useable data that could not be deemed inferior by any other criteria. Instead of using exclusion rules to control the heterogeneity of design, this systematic review followed the recommendation by Stroup *et al.* (2000). Broad inclusion criteria for studies were used and analyses were performed to investigate the effect of study characteristics on the estimated pooled success rates. Despite using broad inclusion criteria, several well designed and executed studies such as those by Strindberg (1956), Ørstavik and Hörsted-Bindslev (1993); Ørstavik *et al.* (1986) and others (Table 1) had to be excluded.

The goal was to explore the available data and partition it to reveal the effect of study characteristics, general patient factors, individual pre-, intra-, and postoperative factors on treatment outcome, whilst triangulating the outcomes of different approaches of exploration.

Preliminary data collection was carried out by two authors (Y-LN and KG) to explore its diversity. Amongst the studies reviewed, there were substantial variations in study characteristics such as sample selection, definition of successful cases, duration after treatment, type and strategy of data collection as well as data analyses. Some of the potential clinical prognostic factors (tooth type, age grouping, size of apical preparation, definition of apical disturbance, apical extent of root filling, quality of root filling and quality of coronal restoration) were sub-classified differently between studies. Therefore, a strategy for pooling the data by recalculation of the available figures was derived. Based on this strategy, a data collection form was designed, tested, refined and adopted. Despite this, disagreement amongst the reviewers existed ($\kappa = 0.57$–0.61). The disagreement could be traced to a lack of clarity in the presentation of methodology and results. For some studies, data had to be extracted from the discussion section where it was sometimes first introduced. When there was a disagreement, an agreement was negotiated between the examiners by presenting the case for each view. In the majority of cases, the source of errors were easily identified and corrected.

The un-weighted pooled success rate by each factor was calculated based on the approach used by Hepworth & Friedman (1997). However, this approach does not take into consideration, the within and between study variations as opposed to the study design-specific weighted pooled success rates estimated using random effects meta-analysis. The discrepancies in the success rates estimated using the two approaches are well demonstrated in Table 4. Therefore, the results based on the un-weighted pooled success rates were not considered in the following discussions. The estimation of pooled success rates for some sub-group analyses within some study characteristics were based on small data sets, restricting their value.

The significant difference in success rates judged by strict or loose radiographic criteria has already been iterated but in addition, the data based on strict criteria revealed a clear trend for differences in the pooled success rates from studies adopting different follow-up durations; for example, 6 month follow-up compared with longer duration. It should be mandatory to state the criteria for success as part of the methodology of future clinical root canal treatment outcome studies, preferably stratified by both loose and strict radiographic criteria. The European Society of Endodontology's (2006) suggest a clinical and radiographic follow-up after at least 1 year with annual recall for up to 4 years before a case is judged a failure. The American Association of Endodontists suggests clinical and radiographic evaluation for a 4- to 5-year period, with the additional proviso of determining the functionality of the treated tooth (http://www.aae.org/dentalpro/guidelines.htm). The origin of this is probably based on the work of Strindberg (1956). From a research perspective and based on this review, the cases should be reviewed for a minimum of 1 year and preferably for at least 3 years, after completion of treatment. It would be preferable to standardize the duration after treatment for all the patients or at least to include the duration as a covariate into the statistical model to account for any variations in the success rate because of the different follow-up times. The best choice of statistical analysis would be to analyse time to healing (success) with survival analysis techniques, however, it would require regular follow-up of all patients. The reality is that the longer the duration of follow-up after treatment, the greater the drop-out rate at recall. Therefore, a balance has to be struck between these competing ideals in both the medical and dental fields, although the use of financial incentives may help improve recall rates (Wang *et al.* 2004).

This review also highlighted two important methodological shortcomings in published root canal treatment outcome studies. The variability in radiographic assessment because of subjectivity in radiograph reading is well recognized (Goldman *et al.* 1972), yet the good practice of employing at least two pre-calibrated observers with intra- & inter-observer agreement tests, was not adopted by most of the studies ($n = 56$). In addition, the statistical methods used for analysing the association between potential influencing factors and treatment outcome, did not take account of the effects of potential confounders.

The overall success rates were not affected by 'year of publication' or 'geographic location of study'. In the former category, the measure of relevance should really be the 'year in which treatment was carried out' but few studies provide this information. Nevertheless, the absence of obvious improvement in success rates by the year of publication suggests that the advances in technology and materials used for root canal treatment do not appear to have influenced treatment outcome significantly. Such a suggestion is strongly refuted by endodontists on the grounds that the apparent lack of improvement in success rates is a function of more adventurous case selection fuelled by confidence in better skills and outcomes. The validity of this proposition is explored further in the second part. For the present, it is argued that the lack of improvement in success rates could be attributed to the fact that, whilst technology has improved instruments and materials to achieve a set of goals, the principles underpinning those goals have not changed over the duration covered by this review (Hall 1928). This brings to the fore, the classic debate about the relative value of biological versus the technical principles in dentistry (Noyes 1922, Naidorf 1972). Noyes (1922) lamented that dentists were not trained to think in biological concepts but to act in mechanical procedures; whilst Naidorf (1972) applauding the technical excellence achieved by the pre-occupation of dentists with this element, deplored the lack of biological awareness of the basic pathology of the problem or the biological consequences of the treatment. The clinical academics in this discipline would probably sustain the validity of these assertions, even today. It is interesting to note that the success rates of studies from the North American countries, where the use of contemporary technology is probably most widely recommended fared no better than those from other countries. Furthermore, the adoption of strict radiographic criteria and microbiological awareness in their approach appeared to bring better results in studies performed in the Scandinavian countries. This speculation is important because it centres around the debates that raged in the 1960s and 1970s about the value of the microbial culture test in informing the progress of treatment, a practice, long as abandoned as unnecessary (Engström *et al.* 1964, Mikkelsen & Theilade 1969, Oliet & Sorin 1969, Morse 1971, Sims 1973, Frank *et al.* 1978, Molander *et al.* 1996a,b). This ultimately led to the adoption of single-visit treatment by many endodontists on the basis of the cost-benefit analysis (Spångberg 2001) an issue that will be explored further in the second part. The historical importance of this biological versus technical debate is important to appreciate, because it fundamentally changed the way root canal treatment was conceived and practiced: from a microbially aware post-focal infection era, to one dominated by a technological awareness but relative microbiological ignorance. The problem of geographical location also merits close inspection, as sometimes, a single study may report pooled data from multi-centre evaluations (Friedman *et al.* 1995).

Although the educational and experience background of the operators had no significant influence on their respective success rates in individual studies, the estimated pooled success rates for endodontists or postgraduates were higher than for other dentist groups in this review. The important influence of the background of operators on the technical outcome of endodontic procedures has been demonstrated in laboratory studies (Gulabivala *et al.* 2000, Van Zyl *et al.* 2005) but there is a lack of appropriate tools or methodology to objectively quantify operator skills. The role of such refined technical skills must surely be balanced against the overall understanding of the problem and the motivation and integrity with which the procedure is performed.

Conclusion

The estimated weighted pooled success rates of treatments completed at least 1 year previously, ranged between 68% and 85% when strict criteria were used. The reported success rates have failed to improve over the last four or five decades. The quality of evidence for treatment factors affecting primary root canal treatment outcome is sub-optimal; there was substantial variation in the study-designs. It would be desirable to standardize aspects of study-design, data recording and

presentation format of outcome data in the much needed future outcome studies. The second part of this paper will present the results of meta-analyses and meta-regression to investigate the effect of individual clinical factors on the success rates of primary root canal treatment.

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REVIEW

Outcome of primary root canal treatment: systematic review of the literature – Part 2. Influence of clinical factors

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Abstract

Ng Y-L, Mann V, Rahbaran S, Lewsey J, Gulabivala K. Outcome of primary root canal treatment: systematic review of the literature – Part 2. Influence of clinical factors. *International Endodontic Journal*, **41**, 6–31, 2008.

Aims (i) To carry out meta-analyses to quantify the influence of the clinical factors on the efficacy of primary root canal treatment and (ii) to identify the best treatment protocol based on the current evidence.

Methodology The evidence for the effect of each clinical factor on the success rate (SR) of primary root canal treatment was gathered in three different ways: (i) intuitive synthesis of reported findings from individual studies; (ii) weighted pooled SR by each factor under investigation was estimated using random-effect meta-analysis; (iii) weighted effect of the factor under investigation on SR were estimated and expressed as odds ratio for the dichotomous outcomes (success or failure) using fixed- and random-effects meta-analysis. Statistical heterogeneity amongst the studies was assessed by Cochran's (Q) test. Potential sources of statistical heterogeneity were investigated by exploring clinical heterogeneity using meta-regression models which included study characteristics in the regression models.

Results Out of the clinical factors investigated, pre-operative pulpal and periapical status were most frequently investigated, whilst the intra-operative factors were poorly studied in the 63 studies. Four factors were found to have a significant effect on the primary root canal treatment outcome, although the data heterogeneity was substantial, some of which could be explained by some of the study characteristics.

Conclusions Four conditions (pre-operative absence of periapical radiolucency, root filling with no voids, root filling extending to 2 mm within the radiographic apex and satisfactory coronal restoration) were found to improve the outcome of primary root canal treatment significantly. Root canal treatment should therefore aim at achieving and maintaining access to apical anatomy during chemo-mechanical debridement, obturating the canal with densely compacted material to the apical terminus without extrusion into the apical tissues and preventing re-infection with a good quality coronal restoration.

Keywords: outcome, root canal treatment, success, systematic review.

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Introduction

Root canal treatment (RCT) may be defined as the combination of mechanical instrumentation of root canal system, its chemical debridement and filling with an inert material, designed to maintain or restore the health of the periradicular tissues. The manner of execution of treatment procedure(s) is so diverse even within prescribed protocols that it is difficult to define it any more precisely and it is accepted that this treatment intervention is not by its nature standardizable. In fact, the procedure is dominated by the tooth in question, in terms of its anatomical complexity and biological status, that is, its pre-operative status. The latter part of the definition alludes to the fact that essentially the same procedure is used to treat two distinct disease entities: (i) the vital but diseased pulp where the goal is to maintain existing periapical health and prevent periapical disease; or (ii) the nonvital or dying pulp associated with periapical disease where the goal is to restore the periradicular tissues back to health. The goal of root canal treatment is therefore to prevent or treat periapical disease; and this simple statement embraces a diverse range of pre-operative and treatment parameters that may or may not all be recorded.

Part 1 of this review has already explored the characteristics of the root canal treatment outcome studies and their effects on the SRs. It was found that there was a substantial variation between studies in their assessment of teeth during follow-up, including the method of radiographic assessment, the radiographic criteria for success (loose and strict), the unit of outcome measure (root and tooth) and the length of follow-up.

The aims of this, part 2 of the systematic review, were (i) to carry out meta-analyses to quantify the influence of the clinical factors on the efficacy of primary root canal treatment and (ii) to identify the best treatment protocol based on current evidence.

Material and methods

In total, 63 studies were included in this part of the systematic review, based on the protocol for literature search, study selection, quality assessment and data extraction described in part 1.

Statistical analyses were performed using the STATA version 9.2 statistical software (Statacorp, College Station, TX, USA). The effects of each clinical factor on the SR of primary root canal treatment were analysed through three different approaches:

1. Intuitive synthesis of reported findings from individual studies. Those studies excluded for the purpose of the statistical analyses were included for this synthesis.

2. Weighted pooled SR by each factor under investigation (all relevant data accumulated from available studies) was estimated using random-effects meta-analysis.

3. Weighted effects of the factor under investigation on SR were estimated and expressed as odds ratio (OR) for the dichotomous outcomes (success or failure) using fixed- and random-effects meta-analysis. This analysis was restricted to studies providing partitioned data on SRs, enabling direct comparison of sub-categories of the factor investigated in the same study.

Statistical heterogeneity amongst the studies was assessed by Cochran's (Q) test. Potential sources of statistical heterogeneity were investigated by exploring clinical heterogeneity using meta-regression models which included study characteristics that were investigated in part 1, as the covariates. If either the estimated proportion of total variation because of the heterogeneity across studies (I^2) or the estimated between-study variance (*tau2*) from the meta-regression model without covariate in the model was reduced substantially (more than 10%), when a covariate was included into the model, the respective covariate was considered to be a potential source of heterogeneity.

Results

Amongst the 63 studies reviewed, none of the studies had evaluated all the clinical factors, consequently, different aspects of data were missing from different studies (Table 1). Pre-selection of individual factors for analysis therefore gave a unique subset of the overall pool of studies that could vary significantly with the combination of factors under scrutiny. For each factor under investigation, the outcomes from each of the three approaches in analysis are reported in their respective section. The estimated pooled SRs by each pre-, intra- and post-operative factor are presented in Tables 2–4. The estimated pooled effects of these factors on the success of treatment are presented in Table 5, whilst the results of meta-regression analyses to explore the source of statistical heterogeneity are presented in Tables 6–8.

Pre-operative factors

Gender

All except two of the previous studies reporting on the influence of this factor ([1]Ingle *et al.* 1965, Adenubi & Rule 1976, Jokinen *et al.* 1978, Ollet 1983, Swartz *et al.* 1983, Smith *et al.* 1993, [2]Friedman *et al.* 1995,

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Table 1 Profile of outcome data by potential prognostic factors by the included studies. (Reproduced from part 1 of this review)

Author (year)	Gender	Age	Health	Tooth type	Pulpal status	Periapical status	Lesion size	Rubber dam	Obstruction	Apical size	Canal taper	Irrigant	Medicament	Culture test	RF material and technique	Sealer	RF extent	Quality of RF	Acute flare up	Apical disturbance	Visits of treatment	Restoration	Abutment
Blayney (1922)					✔	✔		✔				✔											
Auerbach (1938)					✔	✔						✔											
Buchbinder (1941)					✔	✔		✔				✔	✔	✔							✔		
Morse & Yates (1941)					✔	✔		✔				✔		✔							✔		
Castagnola & Orlay (1952)					✔	✔		✔													✔		
Grahnén & Hansen (1961)		✔			✔	✔						✔			✔		✔				✔		
Seltzer *et al.* (1963)					✔	✔								✔	✔		✔						
Zeldow & Ingle (1963)								✔				✔		✔	✔						✔		
Bender *et al.* (1964)					✔	✔								✔	✔		✔				✔		
Engström & Lundberg (1965)					✔								✔	✔							✔		
Harty *et al.* (1970)		✔						✔				✔					✔	✔		✔	✔		
Heling & Tamshe (1970, 1971))					✔	✔		✔				✔	✔			✔	✔						
Cvek (1972)					✔	✔		✔				✔		✔							✔		
Selden (1974)					✔	✔	✔																
Werts (1975)					✔	✔																	
Adenubi & Rule (1976)	✔	✔		✔	✔	✔						✔	✔		✔	✔	✔	✔		✔	✔		
Heling & Shapira (1978)					✔	✔		✔					✔	✔	✔	✔	✔				✔	✔	
Jokinen *et al.* (1978)	✔	✔		✔	✔	✔							✔		✔		✔				✔		✔
Kerekes (1978)				✔											✔		✔	✔					
Kerekes (1978)				✔				✔							✔		✔	✔					
Soltanoff (1978)												✔			✔		✔				✔		
Heling & Kischinovsky (1979)					✔	✔		✔				✔	✔		✔	✔	✔						
Barbakow *et al.* (1980a,b, 1981))		✔		✔	✔	✔		✔					✔		✔	✔	✔				✔		
Cvek *et al.* (1982)					✔	✔		✔	✔			✔			✔								
Nelson (1982)		✔			✔	✔										✔	✔	✔		✔			
Boggia (1983)					✔	✔										✔	✔			✔	✔		
Klevant & Eggink (1983)								✔				✔	✔			✔	✔						
Morse *et al.* (1983a,b,c))					✔	✔						✔	✔		✔		✔				✔		
Oliet (1983)	✔	✔			✔	✔						✔			✔	✔	✔				✔		
Swartz *et al.* (1983)	✔	✔		✔		✔									✔		✔					✔	
Pekruhn (1986)					✔	✔		✔				✔				✔					✔		
Byström *et al.* (1987)					✔	✔		✔						✔	✔		✔				✔		
Halse & Molven (1987)					✔	✔									✔		✔						
Matsumoto *et al.* (1987)					✔	✔	✔	✔					✔	✔			✔				✔		✔
Ørstavik *et al.* (1987) & Eriksen *et al.* (1988)					✔	✔						✔											
Safavi *et al.* (1987)					✔	✔						✔		✔	✔	✔					✔	✔	
Akerblom & Hasselgren (1988)					✔	✔	✔	✔	✔			✔	✔		✔						✔		
Shah (1988)					✔	✔		✔							✔	✔					✔		
Sjögren *et al.* (1990)				✔	✔	✔	✔	✔				✔		✔	✔		✔	✔			✔		
Murphy *et al.* (1991)					✔	✔																	
Cvek (1992)					✔	✔									✔		✔				✔		
Reid *et al.* (1992)								✔					✔		✔	✔					✔		
Jurcak *et al.* (1993)				✔											✔						✔		
Smith *et al.* (1993)	✔	✔			✔	✔		✔			✔				✔	✔	✔				✔		
Peak (1994)				✔	✔	✔									✔		✔						
Friedman *et al.* (1995)					✔	✔						✔	✔		✔	✔							
Çalişken & Şen (1996)			✔		✔	✔	✔	✔				✔	✔		✔	✔				✔	✔		
Ørstavik (1996)					✔	✔		✔				✔											
Peretz *et al.* (1997)		✔			✔	✔																	
Sjögren *et al.* (1997)					✔	✔		✔				✔		✔	✔						✔		
Lilly *et al.* (1998)			✔		✔	✔									✔	✔						✔	
Trope *et al.* (1999)			✔					✔				✔	✔		✔	✔					✔		
Ricucci *et al.* (2000)								✔				✔			✔							✔	
Weiger *et al.* (2000)					✔	✔		✔				✔	✔		✔	✔					✔		
Chugal *et al.* (2001)					✔																		
Deutsch *et al.* (2001)					✔			✔				✔			✔	✔					✔		
Heling *et al.* (2001)					✔	✔						✔				✔	✔	✔				✔	
Peak *et al.* (2001)				✔	✔	✔									✔		✔						
Pettiette *et al.* (2001)					✔	✔																	
Benenati & Khajotia (2002)	✔	✔		✔												✔							
Cheung (2002)	✔	✔		✔	✔	✔		✔					✔		✔	✔					✔		
Hoskinson *et al.* (2002)	✔	✔		✔	✔	✔	✔	✔		✔	✔	✔	✔			✔	✔					✔	
Peters & Wesselink (2002)			✔		✔	✔		✔				✔	✔	✔	✔	✔					✔	✔	
Total	8	13	4	13	51	49	6	33	2	1	2	32	20	14	38	25	29	7	0	5	35	8	2

RF, root filling.

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Hoskinson *et al.* 2002, Cheung 2002, Benenati & Khajotia 2002) did not find any significant association between gender and SR. Swartz *et al.* (1983) & Smith *et al.* (1993) had independently reported root canal treatment in male patients to have a significantly higher SR than in female patients.

Only eight studies (Table 1) provided outcome data by gender. The pooled SRs for male patients were similar to those for female patients regardless of whether loose or strict criteria were used (Table 2). This is consistent with the pooled estimate of effects of gender (OR = 1.01; 95% CI: 0.83, 1.23; Table 5a). The heterogeneity 18.1 (7df, $P = 0.011$) was substantial but could not be explained by any of the study characteristics included in the meta-regression models.

Age

Fifteen studies ([1]Strindberg 1956, Seltzer *et al.* 1963, [1]Ingle *et al.* 1965, Harty *et al.* 1970, Barbakow *et al.* 1980a,b, 1981, Nelson 1982, Oliet 1983, Swartz *et al.* 1983, [1]Ørstavik & Hörsted-Bindslev 1993, Sjögren *et al.* 1990, Smith *et al.* 1993, [2]Friedman *et al.* 1995, Benenati & Khajotia 2002, Cheung 2002, Hoskinson *et al.* 2002) had analysed the influence of patients' age on treatment outcome but found no statistically significant difference in SRs stratified by age. It is noted that the age groups were clustered into bands that varied between studies for the purposes of statistical analyses; direct comparison between studies therefore are required for some degree of intuitive interpretation.

Only 13 (Table 1) studies reported outcome data by age range. For the purpose of this review, the outcome data were pooled into three age bands: up to 25 years, 25–50 years and above 50 years. Although the differences were small, the pooled SRs decreased with increase in age regardless of whether strict or loose criteria for success were used (Table 2). Further meta-analyses showed no significant difference in the odds of success amongst the three age bands (Table 5b). No further meta-regression analyses were carried out as the heterogeneity was not significant.

General medical health

Only one study ([1]Storms 1969) had investigated the influence of the patient's general health on the outcome of root canal treatment and reported no statistically significant difference in SRs between healthy and unhealthy (with known systemic disease) patients. Three studies (Çalişken & Şen 1996, Trope *et al.* 1999, Peters & Wesselink 2002) reported that only healthy patients were included in their studies and three other studies ([1]Markitziu & Heling 1981, [1]Seto *et al.* 1985, Lilly *et al.* 1998) analysed patients who had received radiotherapy in the head and neck region. There was insufficient stratified raw data for calculation of the pooled SRs by this factor.

Tooth type

There was a wide variation in the manner of presentation of outcome data by tooth type in various studies; the descriptors or classification used were: upper/lower teeth, anterior/posterior teeth, anterior/premolar/molar, 1/2/3 roots, 1/≥2 canals or each tooth type.

Thirteen studies ([1]Ingle *et al.* 1965, Heling & Tamshe 1970, 1971, Adenubi & Rule 1976, [1]Selden 1974, Jokinen *et al.* 1978, Barbakow *et al.* 1980a,b, 1981, Oliet 1983, Morse *et al.* 1983a–c, Swartz *et al.* 1983, Pekruhn 1986, [1]Ørstavik & Hörsted-Bindslev 1993, Peak 1994, Peretz *et al.* 1997, Benenati & Khajotia 2002, Cheung 2002, Hoskinson *et al.* 2002) had compared the outcome of treatment between tooth types, statistically. Three studies (Swartz *et al.* 1983, Benenati & Khajotia 2002, Cheung 2002) found statistically significant differences in SRs between tooth types. The former two found that mandibular molars had the lowest SR compared with other tooth types. Smith *et al.* (1993) reported that teeth in the mandibular right quadrant were associated with the lowest SR.

Thirteen studies (Table 1) presented the outcome data by tooth type (maxillary incisor and canine, maxillary premolar, maxillary molar, mandibular incisor and canine, mandibular premolar and mandibular molar); the differences in pooled success between different tooth types were small, the mandibular premolar teeth had the highest SRs whilst the mandibular molar teeth had the lowest SRs based on strict criteria (Table 2). When estimating the pooled effect of tooth type, the outcome data from maxillary and mandibular teeth of the same morphological type were pooled together. The results showed that there was no significant difference in the odds of success amongst the three types of teeth: incisors/canines, premolars and molars (Table 5c). The statistical heterogeneity could be partly explained by the 'criteria of success', 'unit of measure', 'geographic location of the study' and 'year of publication' (Table 6).

Pulpal and periapical status

Comparison of pre-operatively vital and nonvital teeth. Fourteen studies had analysed the influence of

Table 2 Weighted pooled success rates (SRs) by patient factors and pre-operative factors related to the tooth/root

Factor/categories	Total no. of studies[a]	Strict radiographic criteria: No. of studies	No. of units	Weighted pooled SR[c] (%)	Loose radiographic criteria: No. of studies	No. of units	Weighted pooled SR[c] (%)
Gender							
Male	8	5	2200	65.7 (48.3, 83.1)	6	2667	84.9 (75.9, 94.0)
Female	8	5	3044	65.1 (49.9, 80.2)	6	3537	85.2 (75.8, 94.6)
Age							
Below 25	13	7 (6)[b]	2873	68.3 (52.2, 84.4)	8	2243	86.9 (83.2, 90.7)
Between 25 and 50	11	5	2336	66.8 (50.5, 83.2)	7	1813	86.8 (83.2, 90.4)
Above 50	12	5	1159	65.6 (49.8, 81.4)	8	1880	84.1 (78.5, 89.7)
Tooth type							
Upper incisors and canines	13	9	2021	70.6 (54.7, 86.5)	7	2021	85.6 (75.5, 95.7)
Lower incisors and canines	12	8	523	66.6 (47.7, 85.5)	7 (6)[b]	512	85.1 (72.0, 98.3)
Upper premolars	12	8	918	70.1 (56.6, 83.6)	5	711	80.7 (70.4, 91.1)
Lower premolars	10	7	674	76.8 (64.9, 88.6)	5	490	86.2 (76.2, 96.1)
Upper molars	12	8	1327	75.0 (63.6, 86.5)	6	906	83.3 (75.1, 91.5)
Lower molars	11	7	1222	64.2 (47.4, 81.1)	6	1220	81.7 (73.1, 90.3)
Pulpal/periapical (pa) status							
Vital pulp	22	13 (12)[b]	3027	82.5 (74.0, 91.0)	11 (10)[b]	1911	89.6 (83.1, 96.2)
Nonvital pulp	37	23	6343	73.1 (66.1, 80.0)	23	5928	84.7 (80.2, 89.2)
Nonvital pulp without pa lesion	15	9 (8)[b]	1699	82.1 (72.7, 91.6)	7	1141	90.1 (86.9, 93.3)
Nonvital pulp with pa lesion	48	28	4724	69.6 (61.1, 78.1)	29 (28)[b]	6844	81.4 (76.2, 86.6)
Size of periapical lesion							
≤5 mm	6	4	488	80.2 (70.4, 90.0)	3	343	91.0 (84.6, 97.5)
>5 mm	5	3	308	78.8 (74.2, 83.3)	3	362	79.9 (66.1, 93.8)

[a]Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported SRs based on both criteria.
[b]Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% rates by the respective factor under investigation have been excluded.
[c]Weighted pooled SRs were estimated using random-effects meta-analysis (where there was only one study, its reported SR and confident intervals were presented).

pre-operative pulpal status on the treatment outcome, statistically. Four studies (Grahnén & Hansen 1961, [1]Storms 1969, Smith *et al.* 1993, Hoskinson *et al.* 2002) reported that vital teeth had significantly higher SRs than nonvital teeth, but eight studies (Heling & Tamshe 1970, 1971, Adenubi & Rule 1976, Barbakow *et al.* 1980a,b, 1981, Nelson 1982, Morse *et al.* 1983a–c, Oliet 1983, [1]Ørstavik & Hörsted-Bindslev 1993, [2]Friedman *et al.* 1995) had found no such statistical difference. In contrast, [1]Strindberg (1956) & [1]Teo *et al.* (1986) had reported that nonvital teeth had significantly higher SRs than vital teeth with pulpitis. The majority of the studies exploring this variable ($n = 51$; Table 1) provided the SRs by pulpal status of the teeth. The pooled SRs for vital teeth were higher than those for nonvital teeth by 5% (loose criteria) or 9% (strict criteria; Table 2).

Out of the 63 studies reviewed, 19 had stratified SRs for both pre-operative vital and nonvital pulpal states but one study (Morse & Yates 1941) was excluded from the meta-analyses because of the absence of root canal treatment failure in the vital pulp group. The odds of success of vital teeth were 1.77 (95% CI: 1.35, 2.31) times higher than those for nonvital teeth (Table 5d). The heterogeneity in the data was substantial but could not be explained by the covariates investigated in meta-regression models (Table 7a).

Comparison of pre-operatively vital and nonvital teeth without periapical lesion When comparing the pooled

Table 3 Weighted pooled success rates (SRs) by intra-operative factors (a) excluding those related to root fillings and (b) related to root filling

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	Total no. of studies[a]	No. of studies	No. of units	Weighted pooled SR[c] (%)	No. of studies	No. of units	Weighted pooled SR[c] (%)
(a)							
Use of rubber dam isolation							
Yes	31	22	6353	78.0 (72.2, 83.8)	14	3729	84.4 (78.9, 90.0)
No	2	1	335	79.0 (74.6, 83.4)	2	400	82.5 (74.1, 96.4)
Apical size of canal preparation							
Small (ISO 20 – 30)	1	1	351	78.6 (76.4, 80.8)	0	–	–
Large (ISO 35 – 90)	1	1	53	69.8 (63.5, 76.1)	0	–	–
Taper of canal preparation							
Narrow	2	1	200	75.5 (72.5, 78.5)	1	534	82.2 (80.5, 83.9)
Wide	2	1	289	75.1 (72.6, 77.6)	1[b]	287	88.2 (86.3, 90.1)
Irrigant							
NaOCl	20	12	3374	79.3 (72.1, 86.6)	12 (11)[b]	3050	87.8 (82.4, 93.1)
Iodine	1	–	–	–	1	211	96.0 (93.4, 98.6)
Chloramine	1	–	–	–	1	104	63.0 (53.7, 72.3)
H_2SO_4	1	1	1277	82.0 (79.9, 84.1)	0	–	–
Water	2	1	1139	90.0 (88.3, 91.7)	1	42	83.0 (71.6, 94.4)
Saline	3	2	1189	64.4 (18.1, 100)	2	1136	90.3 (84.4, 96.1)
EDTA	3	2	258	72.2 (66.7, 77.6)	1	202	81.0 (75.6, 86.4)
Biosept	1	1	55	94.0 (88.0, 100)	0	–	–
Medicament							
Antibiotics	1	1	859	88.0 (85.8, 90.2)	1	859	95.1 (93.7, 96.6)
Antiseptics excluding calcium hydroxide	9	6	1356	70.2 (55.5, 84.8)	4	671	85.6 (78.0, 93.1)
$Ca(OH)_2$	8	7	1106	75.0 (66.3, 83.8)	4	342	91.0 (86.3, 95.8)
Steroid	3	3	2221	67.5 (41.0, 94.0)	1	2142	67.0 (65.0, 69.0)
Culture before obturation							
Negative	13	9	1523	81.9 (71.6, 92.2)	6	2757	88.2 (83.3, 93.1)
without periapical lesion	*5*	*3*	*372*	*88.6 (85.4, 91.8)*	*3 (2)[b]*	*1142*	*90.9 (86.2, 95.7)*
with periapical lesion	*10*	*7*	*578*	*73.1 (46.3, 100)*	*5*	*1555*	*86.8 (78.2, 95.5)*
Positive	8	4	99	68.5 (58.9, 79.5)	5	793	81.7 (79.0, 84.4)
without periapical lesion	*3*	*2*	*54*	*63.7 (51.0, 76.4)*	*2*	*284*	*91.6 (88.3, 94.8)*
with periapical lesion	*5*	*3*	*45*	*73.6 (61.0, 86.2)*	*3 (2)[b]*	*437*	*75.6 (71.5, 79.6)*
Apical disturbance							
No	4	3	1114	87.0 (82.4, 91.5)	3	1168	88.2 (78.9, 97.5)
Yes	5	3	1043	79.1 (65.5, 92.8)	3	173	72.6 (50.3, 94.9)
No. of visits							
Single	11	6	1077	77.2 (63.8, 90.6)	7 (6)[b]	538	89.5 (86.8, 92.1)
Multiple	30	18	8373	77.4 (69.3, 85.5)	19	7361	85.5 (80.7, 90.2)
(b)							
Root filling material/technique							
Chloropercha	14	11	5766	80.0 (70.3, 91.4)	5	3136	86.9 (72.3, 99.2)
Lateral compaction of GP	23	13 (12)[b]	2986	76.0 (66.6, 85.4)	13	2556	85.8 (81.9, 89.7)
Single GP point	6	2	128	64.4 (56.2, 72.6)	5	2657	84.7 (79.7, 89.7)
Silver point	7	3	220	81.0 (67.0, 94.9)	3	1485	88.4 (83.6, 93.2)
Amalgam	1	–	–	–	1	162	85.2 (79.7, 90.7)
Sealer							
Zinc oxide eugenol-based	13	8	3991	75.3 (63.9, 86.6)	8	3724	86.5 (83.1, 89.9)
Resin-based	8	5	976	70.7 (52.6, 88.7)	5	785	87.3 (76.3, 98.2)
Calcium hydroxide-based	2	2	239	80.2 (75.2, 85.3)	2	239	90.8 (84.9, 96.7)
Glass–ionomer-based	1	1	250	82.4 (77.1, 86.9)	1	250	94.4 (90.8, 96.9)
Endomethasone	1	1	52	60.0 (46.7, 73.3)	1	52	90.0 (81.8, 98.2)

Table 3 (*continued*)

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	Total no. of studies[a]	No. of studies	No. of units	Weighted pooled SR[c] (%)	No. of studies	No. of units	Weighted pooled SR[c] (%)
Apical extent of root filling (RF)							
Teeth with any periapical status							
Short RF	25	13	2106	76.8 (71.3, 82.3)	15	4112	82.5 (78.2, 86.7)
Flush RF	23	13	2874	77.3 (69.6, 85.0)	13 (11)[b]	4305	85.2 (80.0, 90.3)
Long RF	28	16	2599	65.8 (54.1, 77.5)	16 (15)[b]	2567	74.5 (67.9, 81.2)
Teeth with no periapical lesion							
Short RF	5	2	187	93.2 (89.6, 96.8)	3	673	89.9 (82.1, 97.7)
Flush RF	5	2	102	90.4 (77.0, 100)	3	682	92.3 (89.5, 95.2)
Long RF	5	2	180	83.2 (54.4, 100)	3	169	74.2 (67.6, 80.8)
Teeth with periapical lesion							
Short RF	10	4	234	69.9 (61.5, 78.3)	6	801	74.9 (66.1, 83.7)
Flush RF	8	4	331	83.7 (72.7, 94.7)	4 (3)[b]	844	84.2 (78.7, 89.6)
Long RF	11	5	290	73.6 (64.3, 83.0)	6	558	80.8 (70.2, 91.5)
Quality of root filling							
Teeth with any periapical status							
Satisfactory	7	5	2173	87.0 (82.3, 91.7)	3	1076	82.9 (70.4, 95.4)
Unsatisfactory	7	5	427	61.1 (50.4, 71.8)	3	116	64.2 (46.2, 82.1)
Teeth with periapical lesion							
Satisfactory	2	1	193	86.5 (81.7, 91.3)	1	169	63.9 (56.7, 71.1)
Unsatisfactory	2	1	11	81.8 (59.0, 100)	1	23	69.6 (50.8, 88.4)

EDTA, ethylene-diamine-tetra-acetic acid; RF, root filling; GP, gutta-percha.
[a]Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported SRs based on both criteria.
[b]Number in bracket indicating the number of studies included in the meta-analysis after those studies with 100% rates by the respective factor under investigation have been excluded.
[c]Weighted pooled SRs were estimated using random-effects meta-analysis (where there was only one study, its reported SR and confident intervals were presented).

Table 4 Weighted pooled success rates (SRs) by post-operative restorative status of the tooth

		Strict radiographic criteria			Loose radiographic criteria		
Factor/categories	Total no. of studies[a]	No. of studies	No. of units	Weighted pooled SR[b] (%)	No. of studies	No. of units	Weighted pooled SR[b] (%)
Quality of coronal restoration at recall							
Unsatisfactory	6	4	402	60.4 (53.8, 67.1)	2	601	75.6 (56.3, 95.0)
Satisfactory	8	6	763	77.9 (69.7, 86.1)	3	763	85.1 (69.2, 100)
Treated tooth being used as abutment for prosthesis							
Yes	1	–	–	–	1	11	45.5 (30.5,60.5)
No	1	–	–	–	1	74	79.7 (75.0,84.4)

[a]Total number of studies identified for the respective study characteristics is equal to or smaller than the summation of number of studies under strict and loose criteria as some studies reported SRs based on both criteria.
[b]Weighted pooled SRs were estimated using random-effects meta-analysis (where there was only one study, its reported SR and confident intervals were presented).

SRs between vital and nonvital teeth without pre-operative periapical lesion, the difference was <1% regardless of whether strict or loose criteria were used (Table 2).

Out of the 63 selected studies, 11 studies had presented stratified outcome data for both of these pre-operative conditions and were included for estimation of the pooled OR. The odds of success for vital teeth was similar to those for nonvital teeth without periapical lesion (OR = 1.08; 95% CI: 0.69, 1.67; Table 5d). The heterogeneity 33.5 (10 df) was significant. Meta-regression analyses showed that the covariate 'geographic location of study' and 'duration after treatment' were responsible for some of the heterogeneity (Table 7b).

Table 5 Summary of meta-analyses for the effects of clinical factors on success rates of root canal treatment

Comparisons (test versus reference categories)	No. of studies	Odds ratio	95% CI	Heterogeneity χ^2 value	Heterogeneity P value
(a) Gender					
Male versus female	8	1.01	0.827, 1.23	18.1	0.011
(b) Age					
<25 vs. 25–50	10	0.95	0.84, 1.08	11.8	0.226
<25 vs. >50	10	0.96	0.82, 1.12	9.8	0.371
(c) Tooth type					
Premolars versus incisors	10	1.16	0.86, 1.57	29.5	0.001
Molars versus incisors	11	0.92	0.56, 1.51	98.0	<0.001
(d) Effects of pulpal and periapical (pa) status					
Vital versus Nonvital	18	1.77	1.35, 2.31	61.6	<0.001
Vital versus nonvital without pa lesion	11	1.08	0.69, 1.67	33.5	<0.001
Vital versus nonvital with pa lesion	17	2.35	1.77, 3.13	53.6	<0.001
Nonvital without versus with pa lesion	13	1.95	1.35, 2.81	45.8	<0.001
Small versus large pa lesion	5	1.55	0.85, 2.84	11.9	0.018
(e) Effects of pre-obturation culture results					
−ve versus +ve culture results (any pa status)	6	1.17	0.95, 1.44	6.1	0.294
−ve versus +ve culture results (teeth with no pa lesion)	3	1.04	0.65, 1.64	0.9	0.651
−ve versus +ve culture results (teeth with pa lesion)	3	2.12	0.81, 5.53	4.0	0.135
(f) Effects of apical extent of root filling					
Flush versus short (any pa status)	21	1.27	0.93, 1.73	125.0	<0.001
Flush versus short (teeth with no pa lesion)	5	0.83	0.55, 1.23	8.8	0.067
Flush versus short (teeth with pa lesion)	7	1.56	1.26, 1.94	12.0	0.061
Flush versus long (any pa status)	21	2.34	1.87, 2.93	56.1	<0.001
Flush versus long (teeth with no pa lesion)	5	3.72	2.48, 5.60	4.8	0.304
Flush versus long (teeth with pa lesion)	7	1.74	1.36, 2.21	10.2	0.117
Short versus long (any pa status)	24	1.80	1.34, 2.42	117.6	<0.001
Short versus Long (teeth with no pa lesion)	5	2.89	0.89, 9.08	26.3	<0.001
Short versus long (teeth with pa lesion)	9	1.06	0.84, 1.33	14.3	0.075
(g) Quality of root fillings					
Satisfactory versus unsatisfactory	7	3.92	2.26, 6.78	27.6	<0.001
(h) Number of treatment visits					
Single versus multiple (seven studies)	7	1.16	0.82, 1.64	4.43	0.619
Single versus Multiple (three randomized controlled trials)	3	1.89	0.99, 3.63	0.027	0.986
Single versus multiple (three RCTs after excluding cases without pa lesion or not dressed with $Ca(OH)_2$ in multiple visit group)	3	1.35	0.63, 2.88	1.88	0.391
(i) Quality of coronal restorations					
Satisfactory versus unsatisfactory	7	1.82	1.48, 2.25	11.87	0.065

Comparison of pre-operatively vital and nonvital teeth with periapical lesions. The results for this group were in stark contrast to the previous groups; the pooled SRs of vital teeth were 8% (loose criteria) and 13% (strict criteria) higher than those of nonvital teeth with pre-operative periapical lesions (Table 2).

Out of the 63 studies, 18 studies had stratified outcome data by both pre-operative vital teeth versus nonvital teeth with periapical lesion. The paper by Morse & Yates (1941) was not included in the meta-analyses because of the absence of failed cases amongst the vital teeth group, leaving 17 studies in the meta-analysis (Table 5d). The results showed that the odds of success of vital teeth was 2.35 (95% CI: 1.77, 3.13) times higher than nonvital teeth with pre-operative periapical lesion (Table 5d). The heterogeneity 53.6 (16 df) was substantial. However, none of the explored covariates was found to be responsible for the remaining heterogeneity as they neither reduced the I^2 or the *tau2* values when they were entered separately into the meta-regression models (Table 7c).

Table 6 Meta-regression analyses to account for heterogeneity in analysing the effects of tooth type on the success rate of root canal treatment

Covariate included	Proportion of variation because of heterogeneity (I^2)	Estimate of between-study variance (*tau2*)
(a) Comparison of premolars versus incisors (n = 10)		
None	0.70	0.11
Criteria for success (loose or strict)	0.58	0.07
Unit of measure (root or tooth)	0.55	0.08
Geographic location of study (USA, Scandinavian or other countries)	0.20	0.01
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.74	0.16
Duration after treatment (≥4 years or not)	0.70	0.12
Year of publication (before 1970s, 1970–1989, 1990–2002	<0.001	<0.001
(b) Comparison of molars versus incisors (n = 10)		
None	0.90	0.36
Criteria for success (loose or strict)	0.87	0.28
Unit of measure (root or tooth)	0.79	0.20
Geographic location of study (USA, Scandinavian or other countries)	0.15	0.04
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.90	0.37
Duration after treatment (≥4 years or not)	0.90	0.42
Year of publication (before 1970s, 1970–1989, 1990–2002	0.32	0.42

Comparison of pre-operatively nonvital teeth with or without periapical lesion. Ten studies ([1]Engström et al. 1964, [1]Heling & Tamshe 1970, 1971, Adenubi & Rule 1976, Selden 1974, Jokinen et al. 1978, Morse et al. 1983a c, Swartz et al. 1983, Sjögren et al. 1990, [2]Chugal et al. 2001, Hoskinson et al. 2002) had compared the SRs of nonvital teeth/roots with and without periapical lesion statistically, most found the former were associated with significantly lower SRs than the latter. Only Morse et al. (1983a c) could not find a statistical difference.

The above findings are consistent with some studies ([1]Strindberg 1956, Nelson 1982, Matsumoto et al. 1987, Halse & Molven 1987, [1]Ørstavik & Hörsted-Bindslev 1993, Smith et al. 1993, [2]Friedman et al. 1995) that investigated the periapical status without stratifying the pulpal status. [1]Teo et al. (1986) and Peak (1994), however, reported no significant difference in SRs between teeth/roots with or without periapical lesion.

Of the nonvital teeth, the pooled SRs for those without periapical lesions were 9% (loose criteria) and 13% (strict criteria) higher than for those with periapical lesion pre-operatively (Table 2).

Of the 63 studies, 14 studies provided stratified outcome data by both nonvital teeth with and without periapical lesion. The paper by Sjögren et al. (1990) was not included in the meta-analysis because of the absence of failed cases amongst the teeth without pre-operative periapical lesion, leaving 13 studies for the meta-analysis (Table 5d). It was evident that nonvital teeth without periapical lesion had approximately 1.95 (95% CI: 1.35, 2.81) times higher odds of success than nonvital teeth with periapical lesions (Table 5d). The heterogeneity 45.8 (12 df) was substantial and could be partly explained by the 'geographic location of studies' and 'year of publication' (Table 7d).

Size of periapical lesion

Ten studies had statistically compared the SRs of teeth with pre-operative, large or small periapical lesions: six ([1]Storms 1969, Selden 1974, Matsumoto et al. 1987, [2]Friedman et al. 1995, [2]Chugal et al. 2001, Hoskinson et al. 2002) found that teeth with smaller lesions were associated with significantly higher SRs than those with larger lesions. In contrast, [1]Strindberg (1956), Byström et al. (1987) and Sjögren et al. (1990, 1997) found no statistical difference.

Only six reviewed studies (Table 1) provided the outcome data by the size of lesion. By pooling the data for lesion size into <5 or ≥5 mm in diameter, the pooled SR for small lesions was 11% (loose criteria) and 1% (strict criteria) higher than that for large lesions (Table 2). The estimated pooled odds of success for small lesions was higher but not statistically significant when compared with the pooled odds of success for large lesions (OR = 1.55; 95% CI: 0.85, 2.84; Table 5d). The heterogeneity 11.9 (4df, P = 0.018) in the estimate was substantial and could be partly

Table 7 Meta-regression analyses to account for heterogeneity in analysing the effects of pulpal and periapical status on the success rate of root canal treatment

Covariate included	Proportion of variation because of heterogeneity (I^2)	Estimate of between-study variance (*tau2*)
(a) Comparison of vital versus nonvital teeth (n = 18)		
None	0.72	0.22
Criteria for success (loose or strict)	0.74	0.19
Unit of measure (root or tooth)	0.74	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.68	0.26
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.71	0.35
Duration after treatment (≥4 years or less)	0.70	0.23
Year of publication (before 1970s, 1970–1989, 1990–2002	0.71	0.27
(b) Comparison of vital versus nonvital without pa lesion (n = 11)		
None	0.70	0.19
Criteria for success (loose or strict)	0.67	0.24
Unit of measure (root or tooth)	0.72	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.58	0.21
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.61	0.17
Duration after treatment (≥4 years or less)	0.53	0.11
Year of publication (before 1970s, 1970–1989, 1990–2002	0.70	0.21
(c) Comparison of vital versus nonvital with pa lesion (n = 17)		
None	0.70	0.34
Criteria for success (loose or strict)	0.69	0.23
Unit of measure (root or tooth)	0.72	0.39
Geographic location of study (USA, Scandinavian or other countries)	0.74	0.48
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.77	0.74
Duration after treatment (≥4 years or less)	0.72	0.41
Year of publication (before 1970s, 1970–1989, 1990–2002	0.62	0.62
(d) Comparison of nonvital teeth with or without pa lesion (n = 13)		
None	0.74	0.18
Criteria for success (loose or strict)	0.71	0.15
Unit of measure (root or tooth)	0.67	0.24
Geographic location of study (USA, Scandinavian or other countries)	0.65	0.26
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.80	0.33
Duration after treatment (≥4 years or less)	0.69	0.14
Year of publication (before 1970s, 1970–1989, 1990–2002	0.25	0.01
e) Comparison of small and large lesions (n = 5)		
None	0.66	0.27
Criteria for success (loose or strict)	0.65	0.28
Unit of measure (root or tooth)	0.32	0.07
Geographic location of study (USA, Scandinavian or other countries)	0.82	0.78
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	–	–
Duration after treatment (≥4 years or less)	0.32	0.07
Year of publication (before 1970s, 1970–1989, 1990–2002	0.65	0.28

explained by 'unit of outcome measure' and 'duration after treatment' (Table 7c).

Intra-operative factors

Use of rubber dam isolation during treatment

None of the studies on primary root canal treatment had analysed the influence of use of rubber dam isolation on outcome of root canal treatment. Thirty-one studies reported the routine use of rubber dam during treatment whilst only two studies reported that rubber dam was not used. Twenty-eight studies did not mention the use of rubber dam isolation in their treatment protocol. There was no obvious difference in the pooled SRs between the treatments carried out under rubber dam isolation or not (Table 3a). The effects of use of rubber dam isolation could not be analysed further because of insufficient data.

Apical size of canal preparation

Only three studies ([1]Strindberg 1956, [1]Kerekes & Tronstad 1979, Hoskinson *et al.* 2002) have analysed

Table 8 Meta-regression analyses to account for heterogeneity in analysing the effects of apical extent of root filling (RF) on the success rate of root canal treatment

Covariate included	Proportion of variation because of heterogeneity (I^2)	Estimate of between-study variance (*tau2*)
(a) Comparison of flush versus short RF (n = 21)		
None	0.84	0.45
Criteria for success (loose or strict)	0.84	0.47
Unit of measure (root or tooth)	0.83	0.47
Geographic location of study (USA, Scandinavian or other countries)	0.80	0.47
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.71	0.25
Duration after treatment (≥4 years or less)	0.85	0.48
Year of publication (before 1970s, 1970–1989, 1990–2002	0.86	0.62
(b) Comparison of flush versus long RF (n = 21)		
None	0.64	0.18
Criteria for success (loose or strict)	0.64	0.18
Unit of measure (root or tooth)	0.65	0.17
Geographic location of study (USA, Scandinavian or other countries)	0.60	0.17
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.37	0.07
Duration after treatment (≥4 years or less)	0.64	0.16
Year of publication (before 1970s, 1970–1989, 1990–2002	0.65	0.18
(c) Comparison of short versus long RF (n = 24)		
None	0.80	0.43
Criteria for success (loose or strict)	0.81	0.46
Unit of measure (root or tooth)	0.77	0.39
Geographic location of study (USA, Scandinavian or other countries)	0.75	0.36
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.78	0.38
Duration after treatment (≥4 years or less)	0.77	0.42
Year of publication (before 1970s, 1970–1989, 1990–2002	0.79	0.42
(d) Comparison of satisfactory versus unsatisfactory RF (n = 7)		
None	0.78	0.53
Criteria for success (loose or strict)	0.82	0.64
Unit of measure (root or tooth)	0.82	0.64
Geographic location of study (USA, Scandinavian or other countries)	0.78	0.64
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.75	0.40
Duration after treatment (≥4 years or less)	0.80	0.53
Year of publication (before 1970s, 1970–1989, 1990–2002	0.62	0.11
(e) Comparison of satisfactory versus unsatisfactory restoration (n = 7)		
None	0.50	0.09
Criteria for success (loose or strict)	0.57	0.12
Unit of measure (root or tooth)	Insufficient data	
Geographic location of study (USA, Scandinavian or other countries)	0.54	0.11
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.54	0.11
Duration after treatment (≥4 years or less)	0.53	0.11
Year of publication (before 1970s, 1970–1989, 1990–2002	0.41	0.07

the effect of apical size of canal preparation on treatment outcome. Although none of them found any significant influence, both [1]Strindberg (1956) & Hoskinson *et al.* (2002) reported that the SRs decreased with increase of apical size of preparation. The raw data from Hoskinson *et al.*'s (2002) study showed that SR of small (ISO 20–30) apical preparations (77%) was higher than that of large (ISO 35–90) preparations (70%; Table 3a). The effects of size of preparation could not be analysed further because of insufficient data.

Taper of canal preparation

Two studies (Smith *et al.* 1993, Hoskinson *et al.* 2002) analysed the influence of taper of canal preparation on treatment outcome. Smith *et al.* (1993) using loose criteria for determination of success, found that a 'flared' (exact degree of taper was not reported) preparation (wide taper) resulted in significantly higher SRs compared with a 'conical' preparation (narrow taper). In contrast, Hoskinson *et al.* (2002) using strict criteria, did not find any significant difference in treatment outcome between narrow (0.05) and wide (0.10) canal tapers. The SRs stratified by taper of canal preparation are presented in Table 3a. The effect of taper of canal preparation could not be analysed further because of insufficient data.

Canal obstruction and other technical errors
Four studies ([1]Strindberg 1956, [1]Engström *et al.* 1964, Cvek *et al.* 1982, Sjögren *et al.* 1990) have investigated the influence of canal obstruction and other procedural errors on treatment outcome. [1]Engström *et al.* (1964), Cvek *et al.* (1982) and Sjögren *et al.* (1990) found that the presence of canal obstruction resulted in significantly lower SRs, in complete contrast to the findings of [1]Strindberg (1956). Cvek *et al.* (1982) and Sjögren *et al.* (1990) reported that root canal treatment with iatrogenic perforations resulted in significantly lower SRs, whilst [1]Strindberg (1956) found that instrument separation during treatment reduced the SR significantly. None of the studies presented stratified outcome data for the effect of canal obstruction.

Irrigant
Different types of irrigants have been used singly or in various combinations in the studies reviewed, including solutions of: sodium hypochlorite, iodine, chloramine, sulphuric acid, water, saline, ethylene-diamine-tetra-acetic acid (EDTA) solution, hydrogen peroxide, organic acid, Savlon®, Biosept® and quaternary ammonium compound. Some studies ($n = 32$) standardized the use of irrigant, whilst others (10 studies) used a combination of irrigants; 20 studies did not present any information on irrigants. None of the studies has systematically investigated the effect of irrigant on SRs. [1]Cvek *et al.* (1976) found that using 0.5% sodium hypochlorite solution was associated with better healing than using 5% solution after a 3-month canal dressing with $Ca(OH)_2$, but the difference was not statistically significant. The pooled SRs by different irrigants are presented in Table 3a. There was no obvious trend in pooled SRs by the type of irrigant used. The effect of type of irrigant could not be analysed further because of insufficient data.

Medicament
Most studies did not standardize the type of root canal medicament during treatment but the use of a number of medicaments has been reported. In descending order of frequency of reported use, they are: calcium hydroxide ($n = 15$), phenolic compound ($n = 8$), iodine ($n = 4$), creosote ($n = 3$), cresatin ($n = 3$), formaldehyde-based compounds ($n = 3$), corticosteroid ($n = 3$), antibiotics ($n = 2$), Grossman's solution ($n = 1$) and eugenol ($n = 1$). Four studies (Adenubi & Rule 1976, Jokinen *et al.* 1978, Trope *et al.* 1999, Cheung 2002) have investigated the influence of canal medicament on treatment outcome. Adenubi & Rule (1976) found no difference between chloromycetin and neomycin as canal medicament. Jokinen *et al.* (1978) reported that roots treated with a medicament containing corticosteroid had significantly better outcomes than those treated without corticosteroid. Trope *et al.* (1999) found that teeth dressed with calcium hydroxide had significantly higher SRs than those with no dressing. Cheung (2002) concluded that treatment using calcium hydroxide as intra-canal dressing was associated with longer mean survival times than those treatments using Ledermix® or those without medicament dressing at all.

Twenty studies (Table 1) presented the outcome data based on the type of medicament. The pooled SRs of teeth dressed with steroid were lower than those dressed with antibiotics or antiseptics, regardless of whether strict or loose criteria were used (Table 3a). No further analysis was carried out because of insufficient data.

Root canal bacterial culture test results (positive or negative) prior to obturation
Comparison of pre-obturation root canal culture test results regardless of periapical status. Twelve studies have investigated the influence of bacterial culture (prior to obturation) results on treatment outcome; six studies (Buchbinder 1941, [1]Frostell 1963, [1]Engström *et al.* 1964, Engström & Lundberg 1965, [1]Oliet & Sorin 1969, Sjögren *et al.* 1997) found that canals with negative culture results prior to obturation were associated with significantly higher SRs than those with positive culture results. In contrast, the other six studies (Seltzer *et al.* 1963, Bender *et al.* 1964, [1]Storms 1969, Heling & Shapira 1978, Matsumoto *et al.* 1987, Peters & Wesselink 2002) detected no significant difference.

Fourteen studies (Table 1) provided information on treatment outcome related to the bacterial culture test results prior to root canal obturation. The pooled SRs for teeth with negative culture results were higher than those with positive culture results by 7% (loose criteria) and 13% (strict criteria), respectively (Table 3a).

Of the 63 studies initially identified, six studies presented SRs by both positive and negative pre-obturation root canal culture results. The meta-analyses

showed the odds of success of teeth with pre-obturation negative culture were not significantly different from those of teeth with a positive culture (OR = 1.17, 95% CI: 0.95, 1.44; Table 5e). The heterogeneity [6.1 (5 df)] was not significant, therefore, no further meta-regression analysis was carried out.

Comparison of pre-obturation root canal culture test results for teeth without periapical lesion. For those teeth without a pre-operative periapical lesion, the pooled SR of teeth with negative culture results was 1% lower (loose criteria) and 24% higher (strict criteria) than those teeth with positive culture (Table 3a).

Only three studies presented stratified SRs by both culture test results for teeth without periapical lesions. Meta-analysis results showed that there was no significant difference in SRs between teeth with negative or positive culture test results prior to obturation (OR = 1.04, 95% CI: 0.65, 1.64; Table 5e). The heterogeneity 0.86 (2 df) was not significant and therefore, no further meta-regression analysis was carried out.

Comparison of pre-obturation root canal culture test results for teeth with periapical lesions. Interestingly, Bender *et al.* (1964) found that culture results had a significant influence on the outcome of treatment when only the teeth associated with periapical lesions were considered. For those teeth with pre-operative periapical lesion, the pooled SRs of teeth with negative bacterial cultures prior to root filling were 11% higher (loose criteria) and 1% lower (strict criteria), respectively, than those of teeth with positive cultures (Table 3a).

Stratified outcome data were only available from three studies. Although the difference was not statistically significant, the odds of success of those teeth with pre-operative periapical lesion and negative culture were two times (OR = 2.12, 95% CI: 0.81, 5.53) higher than those teeth with periapical lesions and positive culture results (Table 5e). The heterogeneity 4.0 (3 df) was not significant, therefore no further meta-regression analysis was carried out.

Root filling material and technique (single-point gutta-percha, lateral condensation of gutta-percha, silver point, amalgam)
A number of root filling materials have been used in the studies, including: gutta-percha, silver points, amalgam, Hydron® (poly-hydroxyethyl methacrylate), Alytit®, and iodoform paste. Most of the studies obturated the canals using gutta-percha with various types of sealer (24 studies) or gutta-percha softened in chloroform (chloropercha; 14 studies); one study used iodoform paste for obturation of all their cases. Most others (13 studies) used a combination of obturation materials or techniques and ten studies did not present any information on root filling material/technique.

Most of the studies ([1]Strindberg 1956, Seltzer *et al.* 1963, Bender *et al.* 1964, Heling & Tamshe 1970, 1971, Adenubi & Rule 1976, Swartz *et al.* 1983, [1]Teo *et al.* 1986, Reid *et al.* 1992, Peak 1994, [2]Friedman *et al.* 1995) which have investigated the effects of root filling materials/techniques on treatment outcome, did not find any significant influence. There were however some exceptions; Reid *et al.* (1992) found that gutta-percha root fillings were associated with failure significantly less often than Hydron® root fillings. Smith *et al.* (1993) reported that root canals filled with apical amalgam followed by lateral compaction of gutta-percha coronally were associated with significantly higher SRs than those filled with apical amalgam only.

Stratified data on SRs associated with root filling material/technique could be extracted from 38 studies (Table 1) and the pooled SRs are presented in Table 3b. Teeth with chloropercha root fillings were associated with 1% (loose criteria) and 4% (strict criteria) higher pooled SRs than those teeth with lateral compaction of gutta-percha with sealer (Table 3b).

Different types of sealer have been used, including: Zinc oxide eugenol-based (Bioseal®, Grossman® cement, Procosol®, Roth's root canal sealer®), resin-based (AH26®), glass ionomer-based (Ketac Endo®), calcium hydroxide-based (CRCS®, Sealapex®) and Endomethasone®. Zinc oxide eugenol-based sealers (14 studies) or AH26® (eight studies) were the most frequently used. Three studies did not standardize the use of sealer and 34 studies did not report this information. Four studies (Adenubi & Rule 1976, Nelson 1982, Ørstavik *et al.* 1987, Eriksen *et al.* 1988, [1]Waltimo *et al.* 2001) had compared the outcome of treatment using different sealers. Only Nelson (1982) reported that zinc oxide eugenol-based sealers were associated with significantly higher SRs than other sealers (KRI paste®, N2®, Endomethasone®, Spad®) and the others concluded that the type of sealer used had no significant effect on treatment outcome.

The pooled SRs for teeth filled with the resin based-sealer, AH26® had 0.8% higher (loose criteria) and 4.6% lower (strict criteria) SRs than those obturated with zinc oxide eugenol-based sealers (Table 3b). The effects of root filling techniques, materials and type of sealers were not investigated further because of insufficient data.

Apical extent of root filling

Sixteen studies had investigated the influence of apical extent of root filling on treatment outcome. Most of the previous studies classified the various extents into three categories for statistical analyses: >2 mm short of radiographic apex (short), 0–2 mm within the radiographic apex (flush) and extruded beyond the radiographic apex (long). Most found that this factor had significant influence on the SRs: flush root fillings were associated with higher SRs than short root fillings ([1]Strindberg 1956, [1]Storms 1969, Harty *et al.* 1970, Adenubi & Rule 1976, Nelson 1982, Morse *et al.* 1983a–c, Sjögren *et al.* 1990, [1]Ørstavik & Hörsted-Bindslev 1993, Smith *et al.* 1993) or long root fillings ([1]Strindberg 1956, Seltzer *et al.* 1963, Bender *et al.* 1964, [1]Engström *et al.* 1964, Harty *et al.* 1970, Adenubi & Rule 1976, Jokinen *et al.* 1978, Nelson 1982, Swartz *et al.* 1983, Klevant & Eggink 1983, Oliet 1983, Sjögren *et al.* 1990, [1]Ørstavik & Hörsted-Bindslev 1993, Smith *et al.* 1993); short root fillings in turn had significantly higher SRs than long root fillings (Seltzer *et al.* 1963, Bender *et al.* 1964, [1]Engström *et al.* 1964, Adenubi & Rule 1976, Jokinen *et al.* 1978, Nelson 1982, Klevant & Eggink 1983, Oliet 1983, Swartz *et al.* 1983, [1]Teo *et al.* 1986, Matsumoto *et al.* 1987, [1]Ørstavik & Hörsted-Bindslev 1993). Seven studies (Soltanoff 1978, Halse & Molven 1987, Byström *et al.* 1987, Peak 1994, [2]Friedman *et al.* 1995, Sjögren *et al.* 1997, Heling *et al.* 2001, Hoskinson *et al.* 2002) could not find any significant association.

The pooled SRs by apical extent of root fillings revealed the same trends as individual study findings (Table 3b).

Four studies (Bender *et al.* 1964, Halse & Molven 1987, Sjögren *et al.* 1990, Smith *et al.* 1993) had statistically analysed the influence of apical extent of root fillings in teeth with or without periapical lesion, separately. For teeth with no pre-operative periapical lesion, Bender *et al.* (1964) found that flush and short root fillings had similar SRs but had significantly higher SRs than long root fillings. In contrast, Smith *et al.* (1993) reported that the extent of root fillings had no influence on treatment outcome, in agreement with Sjögren *et al.* (1990).

For those teeth with pre-operative periapical lesion, Bender *et al.* (1964) found that flush root fillings had significantly higher SRs, followed by short and then long root fillings. Similarly, Sjögren *et al.* (1990) and Smith *et al.* (1993) also reported that flush fillings had significantly higher SRs than long or short root fillings. In contrast, Jokinen *et al.* (1978) reported that long root fillings had the highest SR followed by flush root fillings and then short root fillings; whilst Halse & Molven (1987) could not detect any significant difference.

The pooled SRs stratified by presence or absence of periapical lesion are presented in Table 3b. When there was no pre-operative periapical lesion, the pooled SRs of long root fillings were the lowest regardless of whether loose or strict criteria were used (Table 3b). When a periapical lesion was present, teeth with flush root fillings had the highest SRs whilst teeth with short root fillings had the lowest SRs (Table 3b).

Meta-analysis to compare flush and short root fillings. Twenty-one studies (Table 5f) presented SRs stratified by short or flush root fillings. The meta-analyses showed that there was no significant difference in the odds of success (OR = 1.27, 95% CI: 0.93, 1.73) between teeth with short or flush root fillings when teeth with or without pre-operative periapical lesion were considered together (Table 5f). The heterogeneity [125.0 (20 df)] was significant and could partly be explained by the 'qualification of operator'. Similarly, no significant difference in the odds of success (OR = 0.83, 95% CI: 0.55, 1.23) was found between flush and short root fillings in teeth without a pre-operative lesion. However, when considering teeth with a pre-operative periapical lesion, those with flush root fillings had 1.6 times the odds of success (OR = 1.56, 95% CI: 1.26, 1.94) compared with teeth with short root fillings. Although the heterogeneity was significant at 10% level, meta-regression analysis was not carried out to explore the source because of insufficient data.

Meta-analysis to compare flush and long root fillings. Twenty-one studies (Table 5f) presented stratified outcome data by long and flush root fillings. The meta-analysis showed that the odds of success for teeth with flush root fillings was significantly higher than those for teeth with long root fillings (OR = 2.34; 95% CI: 1.87, 2.93) when periapical status was not considered (Table 5c). The heterogeneity [56.1 (20 df)] was substantial and could be partly explained by the 'qualification of the operators' (Table 8b). Such a difference in the odds of success remained true even when teeth with or without pre-operative periapical lesions were considered separately in the meta-analyses (Table 5f).

Meta-analysis to compare short and long root fillings. Stratified outcome data by short and long root fillings were available from 24 studies (Table 5f). When teeth with different periapical status were considered together, the meta-analysis results showed that the odds of success for teeth with short root fillings were significantly higher than those for teeth with long root fillings (OR = 1.80; 95% CI:1.34, 2.42; Table 5f). The heterogeneity [117.6 (23 df)] was substantial but none of the tested covariates could account for it as they neither reduced the I^2 or the *tau2* values when they were entered separately into the meta-regression models (Table 8c). When only teeth without pre-operative periapical lesion were considered, the OR increased to 2.89 (95% CI: 0.89, 9.08), with the difference being borderline significant ($P = 0.051$). In contrast, when only teeth with pre-operative periapical lesion were considered, there was no difference in the odds of success between teeth with short or long root fillings (OR = 1.06, 95% CI: 0.84, 1.33; Table 5f).

Quality of root filling

Nine studies had analysed this aspect statistically. Six studies (Harty *et al.* 1970, Adenubi & Rule 1976, [2]Heling & Kischinovsky 1979, Nelson 1982, [1]Teo *et al.* 1986, Halse & Molven 1987) found that satisfactory root fillings were associated with significantly higher SRs than unsatisfactory root fillings ('inadequate seal' or 'radiographic presence of voids'). Cheung (2002) found that voids in root filling present at the mid or apical thirds had significantly worse outcome than those with voids present in the coronal third or those without voids. In contrast, Sjögren *et al.* (1990) and Heling *et al.* (2001) reported that the quality of root fillings had no significant influence on SRs; however, only a small proportion (5–10%) of their cases had unsatisfactory root fillings.

Seven studies provided stratified data by the quality of root filling. The pooled SRs for teeth with satisfactory root fillings were higher than those for teeth with unsatisfactory root fillings by 18.7% (loose criteria) and 25.9% (strict criteria), respectively (Table 3b).

This observation could be confirmed by the large and significant estimated pooled effects (OR = 3.92; 95% CI: 2.26, 6.78; Table 5g). The heterogeneity 27.6 (6 df) in the estimate was substantial and could partly be explained by 'year of publication' (Table 8d).

Apical disturbance during root canal treatment

Various studies have investigated the effect of disturbance of the apical tissues during treatment. 'Apical disturbance' has however, been defined differently by different researchers. Some (Harty *et al.* 1970, Adenubi & Rule 1976, Nelson 1982) defined it as instrumentation beyond the apical foramen or extrusion of sealer/filling. Others only considered extrusion of calcium hydroxide (Çalişken & Şen 1996) or sealer (Boggia 1983, [2]Friedman *et al.* 1995) into the periapical tissue as apical disturbance. There are also conflicting results from their statistical analyses. Harty *et al.* (1970) reported that apical disturbance resulted in a significantly higher SR than absence of apical disturbance, but Adenubi & Rule (1976) reported the contrary. [2]Friedman *et al.* (1995) found extrusion of sealer reduced the SRs significantly. On the other hand, Çalişken & Şen (1996) found that extrusion of calcium hydroxide had no significant influence on the outcome of treatment. Only five studies (Table 1) have provided outcome data based on this factor. The pooled SRs for those cases without apical disturbance were higher than those with apical disturbance by 15.6% (loose criteria) and 7.9% (strict criteria), respectively (Table 3a). No further meta-analyses were carried out because of the difference in definition between studies.

Acute exacerbation during treatment

Sjögren *et al.* (1990) reported that acute 'flare-ups' during treatment had no effects on outcome. None of the studies reviewed has presented outcome data by this factor (Table 1).

Number of treatment visits

Twenty-five studies had carried out all treatments over multiple visits, whilst in four studies all treatment was completed in one visit. In 10 studies, the treatment had been completed in either one or multiple visits, whereas the remainder (22 studies) did not provide this information. All seven studies (Soltanoff 1978, Oliet 1983, Trope *et al.* 1999, Weiger *et al.* 2000, Deutsch *et al.* 2001, Cheung 2002, Peters & Wesselink 2002) comparing the outcome of treatment carried out over single or multiple visits, found no significant difference in SRs between the two approaches. Out of the seven studies, three (Trope *et al.* 1999, Weiger *et al.* 2000, Peters & Wesselink 2002) were randomized controlled trials. Outcome data related to this factor could be extracted from 34 studies (Table 3a). The pooled SRs for single-visit treatment were 4% higher (loose criteria) and

0.2% lower (strict criteria) than the SRs for multiple-visit treatment (Table 3a).

Meta-analysis was initially carried out by incorporating all the seven studies which provided SRs by number of visits. No significant difference in the odds of success (OR = 1.16, 95% CI: 0.82, 1.63) was found and the heterogeneity was not significant (Table 5h). The analysis was repeated after excluding the observational studies, the odds of success for single-visit treatment were higher than those for multiple visit treatment (OR = 1.89; 95% CI: 0.99, 3.63) and the difference was borderline significant (Table 5h). However, in one trial (Trope *et al.* 1999), some of the teeth were not associated with pre-operative periapical lesions and some cases treated over multiple visits had not been dressed with an inter-appointment calcium hydroxide dressing (the main biological purpose of multiple visit treatment). After eliminating such cases, the estimated pooled OR decreased to a statistically insignificant level (OR = 1.35, 95% CI: 0.63, 2.88; Table 5h). Meta-regression analysis was not performed as the heterogeneity was not significant.

Post-operative (root canal treatment) factors

Quality of coronal restoration after RCT

Eleven studies had analysed the influence of quality of coronal restoration on treatment outcome and reported contradicting conclusions. The studies had categorized the quality of restorations differently, for example, restored versus unrestored, satisfactory versus unsatisfactory or permanent versus temporary. Hoskinson *et al.* (2002) defined satisfactory restorations as those with no evidence of discrepancy, discoloration or recurrent caries at the restoration margin with absence of a history of decementation. Some found that root treated teeth with restorations (Heling & Tamshe 1970, 1971, Heling & Shapira 1978, [2]Friedman *et al.* 1995), satisfactory restorations (Swartz *et al.* 1983) or permanent restorations ([2]Heling & Kischinovsky 1979) were associated with significantly higher SRs than their contrary counterpart. In contrast, others ([1]Teo *et al.* 1986, Safavi *et al.* 1987, Ricucci *et al.* 2000, Heling *et al.* 2001, Cheung 2002, Hoskinson *et al.* 2002) found no significant differences.

Eight of the 63 studies (Table 1) had presented outcome data based on quality of coronal restoration after treatment. The pooled SRs for teeth with 'satisfactory' restoration were higher than those teeth with 'unsatisfactory' restorations by 10 and 18% based on loose or strict criteria, respectively (Table 4).

Meta-analysis (Table 5i) incorporating seven studies providing SRs by the quality of coronal restoration showed that the odds of success (OR = 1.82; 95% CI: 1.48, 2.25) were significantly higher in teeth with satisfactory restorations than teeth with unsatisfactory restorations. The heterogeneity 11.9 (6 df) was borderline significant (Table 5i) and could partly be explained by the 'year of publication' (Table 8e).

Use as abutment for prosthesis

Three studies ([1]Storms 1969, Matsumoto *et al.* 1987, Sjögren *et al.* 1990) had investigated the influence of this factor on treatment outcome; however, [1]Storms (1969) had included nonsurgical or surgical re-treatment cases in their analyses of this factor. Sjögren *et al.* (1990) and Matsumoto *et al.* (1987) reported that bridge and denture abutments had significantly lower SRs than individual units, but [1]Storms (1969) did not find such a significant difference. The data for this factor from Matsumoto *et al.*'s (1987) study is presented in Table 4. No further analysis was carried out because of insufficient data.

Discussion

In this study, the authors attempted, *via* a systematic review of observational studies and randomized trials, to explore the effects of individual clinical factors (prognostic and interventions) on the SRs of primary root canal treatment. An ideal clinical intervention outcome study design would include the features of randomization and a control group. The exposure to any prognostic factors and interventions should be easily quantified and recorded and additionally, in the case of interventions, easily delivered in a discrete and standardized manner. In the case of a drug trial, this is relatively easily achieved, the main problem being compliance in delivery. In stark contrast, 'root canal treatment' consists of a series of interdependent steps or procedures including: isolation, access, mechanical preparation of root canals (taper and size of apical enlargement), irrigation, medication and obturation. The mechanical and chemical preparations are delivered in parallel as well as in series, and most importantly, the probability of these factors interacting in their ability to influence outcome is extremely high. It is well known that even a detailed protocol fails to allow two operators to produce the same treatment under identical conditions (Gulabivala *et al.* 2000). Given the variation in pre-operative conditions, the diversity of the cases under treatment is likely to be enormous. The

study of the effect of root canal treatment outcome therefore requires that all relevant factors are recorded or accounted for in detail. In the ideal scenario, the studies (randomized controlled trials) should provide sufficiently detailed data to enable the exploration of the effect of these individual factors and their interactions. In theory, therefore, the estimated weighted pooled ORs and sub-group analyses using the method of meta-analysis should give sufficient information on the effect of individual factors and their interaction on the outcome of treatment. This view is however countered by those who believe a perfect data set is impossible to achieve and mathematical approaches may simply average often incompatible data (Eysenck 1994). It is therefore necessary to include intuitive synthesis to derive an overview, regardless of scientific principles (Popper 1959).

The calculation of ORs requires paired data from the same studies. In the studies reviewed, however, estimated pooled ORs were only possible for 11 factors: 'gender', 'age', 'tooth type', 'pre-operative pulpal status', 'pre-operative periapical status', 'size of periapical lesion', 'pre-obturation culture results', 'number of treatment visits', 'apical extent of root fillings', 'quality of root fillings' and 'quality of coronal restorations'. A number of studies did not provide paired data and therefore in order not to lose these studies from the analyses, the present review included the estimation of *weighted pooled SRs* by each factor, which does not require paired data. In contrast to part 1 of this review, un-weighted pooled SRs were not estimated because they do not take account of the sample size and standard error of individual studies.

Whilst the quality of studies that may be included in meta-analyses has been amply discussed and described, there is an absence of strict guidelines on the minimum number of such studies that should contribute to valid meta-analyses. Some (Janket *et al.* 2003, Stokman *et al.* 2006) meta-analyses have included only two studies of an intervention. Although this is acceptable according to the criteria given by the Cochrane Oral Health Group (personal communication), this is equivalent to calculating variance on two observations, from a statistical point of view. As discussed in part 1 of this paper, the relatively small number of studies included in the meta-analyses to estimate weighted pooled SRs for some factors under investigation may have produced distorted results. For example, the estimated weighted pooled success for those teeth treated without rubber dam, using loose criteria data, had a narrow confidence interval, although the sample size was only two (Table 3a). The SRs reported by the two studies (Barbakow *et al.* 1980a,b, Shah 1988) were not significantly different and had small confidence intervals [90% (87%, 93%) and 78% (68%, 88%), respectively). The study with the larger sample size (Barbakow *et al.* 1980a,b; $n = 335$) and smaller confidence intervals carried more weight in the estimated pooled success value generated by the meta-analysis, thus explaining the final narrow confidence interval.

In general, the results of the meta-analyses showed that there was substantial heterogeneity in the data. Attempts were made to explain the heterogeneity using two approaches: (i) the study characteristics were entered into the meta-regression model as covariates to test their effect on the estimated pooled OR and to evaluate whether their inclusion reduced the proportion of variation because of heterogeneity and the estimate of between-study variance; (ii) sensitivity tests were carried out to test whether the exclusion of studies that did not provide stratified data for primary and secondary treatment would reduce the heterogeneity. The first approach was used to test the study characteristics, of which the following; geographical origin of the study, the decade of publication and qualification of the operators, were found to be responsible for some of the heterogeneity, although not consistently. The second approach was used to test the effect of exclusion of studies that had included re-treatment cases in their data; this did reduce the heterogeneity of the results in the case of studies evaluating the effect of culture results prior to obturation on outcome.

Interestingly, there were greater variations in the weighted pooled estimates of probability of success by each factor based on those outcome data where loose rather than strict criteria for success were used. It is possible that this is because of greater subjectivity in judging partial healing of a lesion than complete healing. It was therefore decided to base the following discussions on the pooled SRs estimated from the data based on the use of strict criteria together with the findings from the intuitive synthesis of individual studies and the estimated pooled effects of factors.

For the general patient factors (gender, age and general medical health), the results of all three analytical approaches were available and all concurred in their findings on the effect of 'gender' and 'age'. The results confirmed that there was no obvious difference in SR between male and female patients, consistent with the fact that there is no known difference in healing potential between genders. Given that presence or absence of pain may be a criterion in the judgement of treatment outcome, the documented difference in pain perception between genders, which has been ascribed to hormonal differences, may have an important bearing on this discussion (Macfarlane *et al.* 2002). Although there was no evidence of significant difference in pooled SRs by the age bands, a trend of pooled SRs decreasing with increase in age was noted. This observation is consistent with the hypothesis that older patients have poorer healing ability because of aging (Mogford *et al.* 2004), malnutrition (Chernoff 2004) or systemic diseases such as diabetes which are more prevalent in the older age group (Cowie *et al.* 2006, Forouhi *et al.* 2006). Although, the evidence for the influence of medical health on treatment outcome is weak based on this review, two studies (Fouad & Burleson 2003, Marending *et al.* 2005), which were published beyond the time-frame for inclusion in this review, reported that diabetes (noninsulin dependent/insulin dependent) or impaired nonspecific immune response had a significant influence on the SRs of root canal treatment on teeth with periapical lesions. Further comprehensive investigations on the effects of age and health as well as their interaction on treatment outcomes are therefore required.

Most studies did not show any significant difference in SRs by tooth type, which was confirmed by the pooled SRs estimated using the meta-analysis method. The results appear to infer that the complex canal anatomy associated with molar teeth does not negatively influence the outcome of root canal treatment. Perhaps more important is the issue of apical anatomy and its infection (Wada *et al.* 1998, Nair *et al.* 2005). The strength of this inference is undermined by the fact that the studies had not stratified the outcome data by pulpal or periapical status per tooth type.

Returning to the issue of absence of obvious improvement in SRs by the year of publication, reported in part 1, the refutation that the apparent lack of improvement in SRs was a function of more adventurous case selection in recent years, may be rebutted on the grounds that tooth type, age, gender and patient's health did not significantly influence outcomes of primary root canal treatment. The outcome of this systematic review may help to inform the designation of case complexity for referral (http://www.aae.org/dentalpro/guidelines.htm, http://www.rcseng.ac.uk/fds/docs/complexityassessment.pdf).

Many pre-operative factors associated with the teeth, such as history of trauma, presence of resorption, presence of fracture or cracks, or presence of swelling and/or sinus, may have an influence on treatment outcome but these have not been systematically investigated in the reviewed studies. Only three factors (pre-operative vitality of teeth, periapical status and size of periapical lesion) were well recorded and researched and results from all three approaches in analysis were available. As alluded to in the introduction, root canal treatment as a treatment intervention is used to manage two distinct biological entities: the diseased but vital pulp with an absence of periapical disease at the one extreme and the necrotic, infected pulp/space with an established periapical lesion, at the other extreme. The problem, however, is more complicated than this, because in reality, the clinician faces a continuous spectrum of pulpal/periapical conditions associated with teeth that can be very difficult to diagnose accurately because of limitations in the sensitivity and specificity of available methods (Dummer *et al.* 1980, Hyman & Cohen 1984). The importance of this lies in the fact that the pulpal and more importantly the periapical conditions have a profound effect on the treatment outcome.

The vitality of pulp was reported as a significant influencing factor by only a small proportion of studies (4/14 studies) that had analysed this factor statistically. Nevertheless, the meta-analysis confirmed that vital teeth had significantly higher SRs (5 9% or OR = 1.8) than nonvital teeth, consistent with the results of meta-analysis by Kojima *et al.* (2004). This demonstrates the value of meta-analyses in increasing statistical power by pooling data from individual studies.

The effect of the interplay between nonvitality and periapical disease on treatment outcome is demonstrated by the following observations. Elimination of data on 'nonvital teeth with periapical lesions' reduced the difference in SRs between 'vital' and 'nonvital teeth' to a negligible level (<0.5% or the OR to 1.1). In contrast, elimination of the data on 'nonvital teeth without periapical lesions', increased the difference in SRs between 'vital' and 'nonvital teeth' to 10% or the OR to 2.4. The important influence of the periapical status was further confirmed by the significant difference (9–13%, OR = 2.0) in SRs between nonvital teeth with and without periapical lesion. The explanation for these clinical observations evidently lies in the knowledge that nonvitality is not always associated with root canal infection (Bergenholtz 1974), whilst the presence of a periapical lesion always signifies the presence of root canal infection (Sundqvist 1976).

The size of the periapical lesion may influence the decision to intervene by both patients and clinicians (Reit & Gröndahl 1984). In this review, all three

analytical approaches showed no significant difference in SRs between small and large lesions. Some of the heterogeneity of the data could be explained by 'unit of outcome measure' and 'duration after treatment'. On the basis of this review, it may be concluded that there is no difference in the outcome of treatment on teeth associated with large or small periapical lesions but the former require longer to heal completely; their evaluation therefore requires a longer follow-up period.

In contrast to the pre-operative data, that on intra-operative factors was comparatively deficient; the reviewers could usually only call on one or two of the three analytical approaches for most factors. Even when the results from two approaches were available, the synthesis was compromised by the small number of studies available. Definitive conclusions could therefore not be drawn on most of the following factors: use of rubber dam, canal obstruction and procedural errors, apical size and taper of canal preparation, type of irrigants, root filling material/technique, type of medicaments and sealer and apical disturbance during treatment. The treatment aspects on which reasonable data were available included: 'pre-obturation culture results', 'apical extent of root fillings', 'quality of root filling', 'quality of coronal restoration' and 'number of treatment visits'.

The pre-obturation culture was putatively designed to detect residual bacteria in the root canal system in the hope that it would be a good predictor for treatment outcome. In reality it is probably a better measure of the efficacy of bacterial removal from the *prepared part* of the root canal system. It is likely that the infection in the apical anatomy would be better correlated to treatment outcome (Goria *et al.* 2005, Nair *et al.* 2005). The root canal bacterial sampling and detection techniques have varied between studies and in their ability to detect residual apical infection. This may partly explain the inconsistent reports from individual studies with only half (6/12) of the studies finding that culture results had a significant effect on treatment outcome. In contrast, the pooled SRs of teeth with negative culture were 7–13% higher than those teeth with positive cultures. After excluding those studies that had not partitioned the re-treatment cases as well as those that had not provided paired sets of data, only 6 of the 12 studies remained to contribute to the estimation of the pooled effect of this factor on outcome. Although the results of both approaches of analyses (estimation of pooled SRs and pooled OR) were in favour of a negative pre-obturation culture result, the estimated pooled effect [OR = 1.2; 95% CI: 0.95, 1.44; chi-square for heterogeneity 6.1 (5 df) $P = 0.294$] was not statistically significant. This could however be attributed to a lack of statistical power. In order to formally justify the exclusion of studies that had not partitioned re-treatment cases, the meta-analysis was repeated by including this data ($n = 14$ studies). On doing so, the estimated effect of pre-obturation culture results (OR = 1.9, 95% CI: 1.4, 2.7) became highly significant ($P < 0.001$) but the heterogeneity also became substantial 30.7 (13 df, $P = 0.004$). This highlights the dilemma in where to set the boundary between inclusion and exclusion criteria for studies in systematic reviews. The use of strict inclusion criteria may reduce the number of incorporated studies and heterogeneity but also the statistical power in detecting significance of the factor under investigation as well as that of the heterogeneity. Attempts were made to further analyse the effect of culture results by teeth with or without pre-operative periapical lesion but the pooled SRs (Table 3a) and the ORs (Table 5e) gave contradictory results. This was because of the small number of studies incorporated in the analyses and a large discrepancy in the number of units in each category. This showed that the adopted principle of triangulation of outcomes through different analytical approaches has merit.

Apart from bacterial culture results, other treatment measures that may serve as surrogate measures of root canal treatment efficacy, include the apical extent of instrumentation and root fillings. Whilst the measure 'apical extent of root filling' was frequently measured, none of the selected studies had analysed the influence of apical extent of instrumentation. Therefore, in the absence of such information, the 'apical extent of root fillings' may serve as a crude and imprecise surrogate measure of the 'extent of instrumentation'. The use of the radiographic root apex as the reference point for measuring the apical extent of root filling in previous studies has been criticized because of the poor correlation between the location of this point and the actual canal foramen (Mizutani *et al.* 1992).

The effect of apical extent of root fillings on treatment outcome was profound and interacted with the periapical status. All three analytical approaches concurred that: teeth with flush root fillings had the highest SRs followed by short and then long root fillings, in agreement with Kojima *et al.* (2004). However, the difference between flush and short root fillings was small and not significant (OR = 1.27, 95% CI: 0.93, 1.73). The results of the analyses stratified by presence or absence of periapical lesion were compromised by the substantially smaller number of studies contributing to the data and have to be interpreted with caution. Nevertheless, the results showed that the difference in SRs between teeth with flush and short root fillings was not significant when the teeth were not associated with periapical lesions. In contrast, the difference in SRs between teeth with short and long root filling was not significant when the teeth were associated with periapical lesions. On the basis of these findings, it may be speculated that both the apical extent of instrumentation and root filling had significant effects on outcome. These two factors may interact with each other as it is generally normal practice to obturate the canal to the same extent as canal preparation. Explanation of these observations lie in the fact that a single measure 'apical extent of root filling' informs about both the apical extent of canal cleaning, as well as the potential extrusion of foreign materials into the surrounding tissues. Extrusion of cleaning, medication or filling materials beyond the apical terminus into the surrounding tissues may result in delayed healing or even treatment failure because of a foreign body reaction (Yusuf 1982, Nair *et al.* 1990, Koppang *et al.* 1992, Sjögren *et al.* 1995).

The radiographic measure of 'quality of root filling' could be used as an indicator of the ability of the root filling to prevent root canal system re-infection or as a surrogate measure of the quality of the entire root canal treatment delivered by the clinician. Unfortunately, the criteria for judging the quality of root fillings have not been well defined by the selected studies. Satisfactory root fillings were defined either as having 'adequate seal' or 'radiographic absence of voids'. This subjective assessment has not been standardized or calibrated, nor tested for variability in assessment by inter- and intra-observer agreement. Nevertheless, all three analytical approaches showed that 'unsatisfactory' root fillings had significantly lower SRs than those judged 'satisfactory'; so perhaps, the intuitively judged crude measure was adequate for the purpose.

There has been an on-going controversy, fuelled by debate between specialists arguing for single-visit treatment on the basis of cost-effectiveness and business sense against academics and some specialists arguing for multiple visit treatments, based on a biological rationale (Spångberg 2001). The main thread of argument for multiple visit treatments is the putative desirability of using an inter-appointment calcium hydroxide dressing for its antibacterial effect and to gauge the periapical response before root filling. The results of all three analytical approaches showed no significant difference in the SRs between treatments carried out over one or multiple visits, in agreement with the review by Sathorn *et al.* (2005). Their meta-analysis only included three randomized controlled trials and only those cases treated with calcium hydroxide were included in the multiple visit treatment dataset. They commented on the lack of power in the three studies as well as in the pooled data, as a sample size of 433–622 was deemed necessary for a difference in 10% SR in such a trial.

The importance of the post-root canal treatment coronal restoration was supported by two quantitative analytical approaches and showed that teeth with satisfactory coronal restorations had significantly better periapical healing (10–18%; OR = 1.82) compared with those with unsatisfactory restorations. On the basis of these results, the provision of the coronal restoration should be considered the final part of the root canal treatment procedure along with obturation to prevent post-operative re-infection.

Within the limitations of this systematic review, four factors have been identified as having a strong effect on the outcome of root canal treatment on the evidence from at least two of the three analytical approaches. These included: (i) presence of periapical lesion, (ii) apical extent of root filling, (iii) quality of root filling and (iv) post-treatment restorative status. The relative strength of effect of each factor and the potential interactions between them could not be precisely determined because of the lack of sufficient data. The interactions between the periapical status and each of the significant treatment factors have, however, been demonstrated to some degree. The main clinical inference is to focus canal preparation on obtaining and maintaining access to the apical anatomy (infection) particularly in the presence of a pre-operative periapical lesion. Once the access to the apical anatomy has been achieved, care should be taken to decontaminate the canal system and then to provide a filling extending from the terminus of the root canal system to the coronal access, in order to prevent re-infection. Although the quality of the root canal treatment should not be judged purely by the radiographic appearance of the root filling, it could be used as a surrogate measure of the extent and quality of the entire treatment. Instrumentation and obturation should be extended to the terminus of the root canal system without extruding materials into the surrounding tissues. The significant effects of the quality of the coronal restoration warrant its immediate placement or

at least some sort of a permanent (antibacterial) seal in the access cavity.

There is, however, a lack of evidence to guide clinicians in the selection of the best decontamination and root canal obturation protocols. There is, therefore, a need to carry out further randomized controlled trials to identify the most appropriate size, taper and extent of canal preparation, irrigation regime (type of irrigant and method), medication regime (type and method) and root filling material and technique, in order to improve the probability of success of root canal treatment. Complete randomization of samples is often not effective in reducing imbalance of pre-operative prognostic factors but may be improved by stratified randomization (Lewsey 2004). The design of randomized controlled trials for root canal treatment is further complicated by the fact that not all sources of clinical heterogeneity (intra-operative factors) can be identified and quantified. Examples of immeasurable or nebulous factors include: the complexity of the root canal system and access to it; the clinical and technical skills of the operator; the logistical, organizational and delivery aspect of the care and the patient's healing capacity. In addition, the interactions between the treatment factors cannot be ignored. A number of examples may be cited: (i) the size and taper of the canal preparation influences the efficacy of the irrigation regime to remove a bio-molecular film from the root canal system (Ng *et al.* 2006); (ii) certain root canal obturation techniques require a larger apical size and taper of canal preparation (Schilder 1967); and (iii) the use of thermo-plasticized root canal obturation techniques may result in higher prevalence of root filling extrusion (Van Zyl *et al.* 2005). When designing an outcome study, a robust decision is therefore required on the potential confounding factors that would be controlled/standardized *versus* those that would be recorded. The statistical analyses used should also respect the hierarchy that is often inherent in clinical data, and should partition the total variation within the data across 'levels' accordingly. For the endodontic treatment dataset, the individual roots (level 1) are nested within the tooth (level 2), and the individual teeth are nested within the patient (level 3). These issues have never been addressed in previous endodontic outcome studies. Last but not least, further root canal treatment outcome studies should standardize the pre-operative pulpal and periapical status of teeth and account for known confounders, such as quality and apical extent of root fillings and quality of coronal restorations, review all the treatments for at least 3 years, report the stratified SRs by strict and loose criteria, and use more than two pre-calibrated radiographic observers with intra- and inter-observer agreement tests. The inference is that a complex treatment intervention such as root canal treatment requires a complex system for recording the procedure characteristics. Unfortunately, no automated recording system exists and requires at least a two-step (observation followed by recording) system that has to be manually operated. This can have unfavourable effects on compliance in data recording (Saunders *et al.* 2000); it is therefore important to rationalize and prioritize essential data for collection. The present review outcomes should help inform both study design and prioritization of factors for recording.

In conclusion, the results of this review should be interpreted with caution and cannot be considered to give definitive conclusions because of the retrospective and heterogeneous nature of the data. It does, however provide strong clues about the factors likely to dominate outcomes and inform the design of future randomized controlled trials.

Notes

1. Studies excluded for reasons given in Table 1.
2. Re-treatment cases were included in the stratified data by potential influencing factors.

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REVIEW

Outcome of secondary root canal treatment: a systematic review of the literature

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Abstract

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Aims (i) To investigate the effects of study characteristics on the reported success rates of secondary root canal treatment (2°RCT or root canal retreatment); and (ii) to investigate the effects of clinical factors on the success of 2°RCT.

Methodology Longitudinal human clinical studies investigating outcome of 2°RCT which were published upto the end of 2006 were identified electronically (MEDLINE and Cochrane database 1966–2006 Dec, week 4). Four journals (*Dental Traumatology, International Endodontic Journal, Journal of Endodontics, Oral Surgery Oral Medicine Oral Pathology Endodontics Radiology*), bibliographies of all relevant papers and review articles were hand-searched. Two reviewers (Y-LN, KG) independently assessed and selected the studies based on specified inclusion criteria and extracted the data onto a pre-designed proforma, independently. The criteria were: (i) Clinical studies on 2°RCT; (ii) Stratified analyses available for 2°RCT where 1°RCT data included; (iii) Sample size given and larger than 10; (iv) At least 6-month post-operative review; (v) Success based on clinical and/or radiographic criteria (*strict = absence of apical radiolucency; loose = reduction in size of radiolucency*); and (vi) Overall success rate given or could be calculated from the raw data. Three strands of evidence or analyses were used to triangulate a consensus view. The reported findings from individual studies, including those excluded for quantitative analysis, were utilized for the intuitive synthesis which constituted the first strand of evidence. Secondly, the pooled weighted success rates by each study characteristic and potential prognostic factor were estimated using the random effect model. Thirdly, the effects of study characteristics and prognostic factors (expressed as odds ratios) on success rates were estimated using fixed and random effects meta-analysis with DerSimonean and Laird's methods. Meta-regression models were used to explore potential sources of statistical heterogeneity. Study characteristics considered in the meta-regression analyses were: decade of publication, study-specific criteria for success (radiographic, combined radiographic & clinical), unit of outcome measure (tooth, root), duration after treatment when assessing success ('at least 4 years' or '<4 years'), geographic location of the study (North American, Scandinavian, other countries), and qualification of the operator (undergraduate students, postgraduate students, general dental practitioners, specialist or mixed group).

Results Of the 40 papers identified, 17 studies published between 1961 and 2005 were included; none were published in 2006. The majority of studies were retrospective (n = 12) and only five prospective. The pooled weighted success rate of 2°RCT judged by complete healing was 76.7% (95% CI 73.6%, 89.6%) and by incomplete healing, 77.2% (95% CI 61.1%, 88.1%). The success rates by 'decade of publication' and 'geographic location of study' were not significantly different at the 5% level. Eighteen clinical factors had been investigated in various combinations in previous studies. The most frequently and thoroughly investigated were 'periapical status' (n = 13), 'size of lesion' (n = 7), and 'apical extent of RF' (n = 5) which were found to be significant prognostic factors. The effect of different aspects of primary treatment history and re-treatment procedures has been poorly tested.

Conclusions The pooled estimated success rate of secondary root canal treatment was 77%. The presence of pre-operative periapical lesion, apical extent of root filling and quality of coronal restoration proved significant prognostic factors with concurrence between all three strands of evidence whilst the effects of 1°RCT history and 2°RCT protocol have been poorly investigated.

Keywords: meta-analysis, outcome, root canal re-treatment, success, systematic review.

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Introduction

A number of studies specifically evaluating clinical outcome of root canal re-treatment [secondary root canal treatment (2°RCT)] have been published in the literature since the comprehensive reports by Bergenholtz *et al.* (1979a,b). There is a general belief that the success rates for 2°RCT are lower than those for primary treatment (Selden 1974, Pekruhn 1986, Sjögren *et al.* 1990, Friedman *et al.* 1995) but this is not universally supported (Molven & Halse 1988, Chugal *et al.* 2001). At the time of writing, there was only one systematic review (Paik *et al.* 2004) examining the level of evidence for the outcome of 2°RCT. The effect of study characteristics and the effect of individual clinical factors on 2°RCT outcome have not been investigated systematically. Such information would be useful for guiding clinical decision-making on re-treatment options as well as to inform the design of future randomized controlled trials on 2°RCT. The lack of randomized controlled trials for 2°RCT (Paik *et al.* 2004) should predict a substantial statistical heterogeneity due to variation in study designs, therefore this systematic review adopted the approach previously used for primary root canal treatment (1°RCT) (Ng *et al.* 2007), that is to use a process of 'triangulation' of three different analytical approaches.

The aims of this systematic review were: (i) to investigate the effects of study characteristics on the reported success rates of secondary root canal treatment (2°RCT or root canal re-treatment); and (ii) to investigate the effects of clinical factors on the success of 2°RCT.

Materials and methods

Literature search

Longitudinal clinical studies investigating the outcome of secondary root canal treatment that were published upto December 2006 were identified electronically (MEDLINE database 1966–2006 Dec, week 4) using 5 keywords (1. root canal re-treatment, 2. endodontic re-treatment, 3. endodontics, 4. treatment outcome, 5. success) and 6 strategies (1 AND 4, 1 AND 5, 2 AND 4, 2 AND 5, 3 AND 4, 3 AND 5). A Cochrane Library search was also conducted. PubMed was independently searched using the 'related articles' feature. Four journals (*Dental Traumatology, International Endodontic Journal, Journal of Endodontics, Oral Surgery Oral Medicine Oral Pathology Endodontics Radiology*), bibliographies of all relevant papers and review articles were hand-searched. Unpublished studies were identified by searching abstracts and conference proceedings. Personal contacts were also used to identify ongoing or unpublished studies. Full articles were obtained for all the titles and abstracts (when available).

Study selection, quality assessment and data extraction

Two reviewers (Y-LN, KG) independently assessed and selected the studies based on the following inclusion criteria:

1. Clinical study on secondary root canal treatment;
2. Stratified analyses available if primary root canal treatment cases had been included;
3. Sample size given and larger than 10;
4. At least a 6-month post-operative review;
5. Success based on clinical and/or radiographic (strict = absence of apical radiolucency; loose = reduction in size of radiolucency) criteria;
6. Overall success rate given or could be calculated from the raw data.

Disagreements on study inclusion were resolved by discussion. The reasons for study rejection at this or subsequent stages were recorded.

Data were extracted by two reviewers independently using custom-designed data collection forms. The data collection form had been piloted on several papers and modified for optimal utility before final use. The data extracted could be classified into six groups: success rates, study characteristics, patient demographic data, pre-, intra- and post-operative factors. Any disagreement was discussed and data were excluded if agreement could not be reached.

Data analyses

Pooled success rates and the influence of study characteristics

Stata version 9.2 statistical software (StataCorp LP, College Station, TX, USA) was used to perform all statistical analyses. The weighted pooled success rates were estimated using random effects meta-analysis with DerSimonian and Laird's methods (DerSimonian & Laird 1986). The effect of study characteristics on the pooled success rates were investigated by entering each factor as a covariate in the regression model. The study characteristics investigated were: decade of publication; study-specific criteria (radiographic, combined radiographic & clinical) for success, unit of outcome measure (tooth, root); duration after treatment when success was assessed ('at least 4 years' or '<4 years'); geographic location of the study (North American, Scandinavian, other countries); and qualification of the operator (undergraduate students, postgraduate students, specialist or mixed group).

Effects of clinical factors

The effects of various aspects of 2°RCT on success rate were analysed through three approaches:

1. Intuitive synthesis of reported findings from individual studies. Those studies excluded for the purpose of the statistical analyses, were included for this synthesis.

2. Weighted pooled success rate by each factor under investigation was estimated using random effects meta-analysis with DerSimonian and Laird's methods. In cases where data were only available from one study, the study reported success rate and 95% confidence interval was used.

3. Weighted effects (expressed as odds ratio) of these factors on success rates were estimated using fixed and random effects meta-analyses with DerSimoncan and Laird's methods. Statistical heterogeneity amongst the studies was assessed by Cochran's (Q) test. Meta-regression models were used to explore any sources of statistical heterogeneity amongst the study characteristics. This analysis was only performed when success rates, stratified by clinical factor under investigation, were available from more than two studies.

Results

In total, 40 articles that had reported the outcome of 2°RCT, were identified and 21 were excluded for various reasons (recorded in Table 1). Some papers presented different parts of the same study; therefore their data were combined for analyses: (1) Bergenholtz *et al.* (1979a,b), (2) Molven & Halse (1988) & Fristad *et al.* (2004).

Table 1 Reasons for exclusion of the 21 studies

Article	Excluded because following condition not met
1. Puterbaugh (1926)	Overall success rate could not be calculated
2. Rhein *et al.* (1926)	At least 6-month post-operative review
3. Appleton (1932)	At least 6-month post-operative review, same data set as Rhein *et al.* (1926)
4. Buchbinder (1936)	Overall success rate could not be calculated
5. Strindberg (1956)	No stratified data for re-treatment cases
6. Frostell (1963)	No stratified data for re-treatment cases
7. Ingle *et al.* (1965)	No stratified data for re-treatment cases
8. Storms (1969)	Only 4 cases
9. Heling & Kischinovsky (1979)	Only 6 teeth
10. Kerekes & Tronstad (1979)	Overall success rate could not be calculated
11. Cheung (1993)	Not a clinical study
12. Gutknecht *et al.* (1996)	No stratified data for re-treatment cases
13. Hepworth & Friedman (1997)	Not a clinical study
14. Kvist & Reit (1999)	Overall success rate could not be calculated
15. Kvist & Reit (2000)	Not measuring clinical/ radiographic success
16. Fava (2001)	Not a clinical study
17. Hoen & Pink (2002)	Not measuring clinical/ radiographic success
18. Main *et al.* (2004)	Overall success rate could not be calculated (only considered healing of lesions at the perforation site)
19. Marending *et al.* (2005)	No stratified data for re-treatment cases
20. Spili *et al.* (2005)	No stratified data for re-treatment cases
21. De Quadros *et al.* (2005)	No stratified data for re-treatment cases

Methodological characteristics of included studies

The 17 selected studies were published between 1961 and 2005 (Table 2); none were published in 2006. Most were retrospective studies and only five were prospective cohort studies, of which one (Danin *et al.* 1996) was a randomized controlled trial comparing the outcome of surgical and nonsurgical re-treatment of teeth with failed 1°RCT. The recall rates (percentage of patients attending for follow-up after treatment) were reported by 16 studies and ranged from 20% to 100% with a median of 73.5%. Either root ($n = 7$) or tooth ($n = 10$) was used as the unit of outcome measure. The sample size ranged from 18 to 452 teeth and 76 to 612 roots.

The treatment outcome was determined by radiographic examination alone (three studies) or in combination with clinical findings (14 studies) (Table 2). Most studies ($n = 14$) used strict radiographic criteria (complete resolution of periapical lesion at recall) for determination of success and eight studies followed up all the cases for at least 4 years (Table 2).

For the radiographic assessment of the outcome of treatment, 13 studies (Table 2) employed at least two observers to carry out the assessment. Observer(s) were calibrated prior to evaluation of radiographs in nine studies and intra- or inter-observer reliability tests were carried out in nine studies (Table 2).

The statistical methods used for analysing the association between potential influencing factors and treatment outcome were the chi-square test (10 studies), logistic regression models (three studies), Mann Whitney *U*-test (one study), and logistic regression models using generalized estimating equations (one study) (Table 2). Two studies did not analyse the data statistically or did not present such information.

Success rates by study characteristics

Assessment of outcome and criteria for success

The reported success rates in individual studies ranged from 28% to 90% with a median of 79%. When stratifying the data by 'strict' or 'loose' criteria, the ranges were 62% to 90% based on strict criteria and 28% to 93% based on loose criteria. The pooled weighted success rate from data based on 'strict' criteria (data available from 14 studies) [76.7% (95% CI: 73.6%, 89.6%)] (Fig. 1) was similar to that from data based on 'loose' criteria (data available from eight studies) [77.2%, (95% CI: 61.1%, 88.1%)] (Fig. 2). Some studies provided outcome data by both criteria. For the data based on strict criteria, the pooled success rates by the method of assessment (radiographic & clinical examination versus radiographic examination alone) were similar. However, using loose criteria for determination of success, there was a substantial difference in the pooled success rate based on radiographic & clinical examination (83%) compared with that based on radiographic examination alone (28%) (Table 3). Notably, there was only one study contributing to the latter dataset (Table 3).

Duration of follow-up after treatment completion

Most studies did not standardize duration of review after treatment which ranged from 6 months to 20 years. Attempts to pool data on success rates by different follow-up durations were confounded by either no data or relatively small number of studies in most groups, rendering comparisons less meaningful (Table 3).

Year of publication

The data for outcomes stratified by decades are presented in Table 3. The pooled success rates for treatments carried out in the "2000's" appeared to be the lowest ($P < 0.05$) regardless of whether 'Strict' or 'Loose' outcome criteria were used.

Geographic location of study

About 40% of the studies were carried out in Scandinavian countries (seven studies, Sweden/Norway) and the rest were carried out in North American (USA/Canada) (five studies) or other countries (five studies) including: UK [1], Belgium [1], Italy [1], Saudi Arabia [1], and Turkey [1]. In one study (Friedman *et al.* 1995), the treatments were carried out in USA, Germany or Israel (Table 2). Based on the loose criteria, the pooled weighted estimate of success rate of treatment carried out in Scandinavian countries (56%) was much lower than in North American (85%) and other (81%) countries. In contrast, the pooled estimate of success rate from outcome data based on strict criteria from the Scandinavian countries (82%) was higher than that from the North American countries (75%) (Table 3). Meta-regression analyses revealed the geographic location of study did not have a significant influence on the success rates of 2°RCT on teeth with ($P = 0.1$) or without ($P = 0.2$) pre-operative periapical lesion.

Table 2 Study characteristics

Study ID	Authors	Geographic location	Operator	Study design	Recall rate (%)	Sample size (units)	Unit of measure	Assessment of success	Radiographic criteria of success	≥4 year after treatment	≥2 radiographic observers	Calibration	Reliability test	Statistical analysis
1	Grahnén & Hanssen (1961)	Sweden	UG	R	64	502	Ro	C&R	S	✔	✔	–	–	–
2	Engström *et al.* (1964)	Sweden	UG	R	72	153	T	C&R	L	✔	✔	–	–	χ^2
3	Selden (1974)	USA	Sp	R	20	52	T	C&R	L	–	–	–	–	χ^2
4	Bergenholtz *et al.* (1979a,b)	Sweden	UG	R	66	556	Ro	C&R	S	–	✔	–	✔	–
5	Pekruhn (1986)	Saudi Arabia	Sp	R	81	36	T	C&R	S	–	–	–	–	χ^2
6	Molven & Halse (1988) & Fristad *et al.* (2004)	Norway	UG	R	50	226	Ro	Ra	S	✔	✔	✔	✔	χ^2
7	Allen *et al.* (1989)	USA	–	R	53	315	T	C&R	S	–	–	✔	–	χ^2
8	Sjögren *et al.* (1990)	Sweden	UG	R	46	267	Ro	C&R	S	✔	✔	✔	✔	LR
9	Van Nieuwenhuysen *et al.* (1994)	Belgium	–	R	–	612	Ro	C&R	S	–	✔	✔	✔	χ^2
10	Friedman *et al.* (1995)	Canada[a]	Sp	C	78	128	T	C&R	S	–	–	–	–	χ^2
11	Danin *et al.* (1996)	Sweden	Sp	RCT	100	18	T	Ra	L	–	✔	✔	✔	χ^2
12	Sundqvist *et al.* (1998)	Sweden	UG	C	93	50	T	C&R	S	✔	✔	–	–	χ^2
13	Chugal *et al.* (2001)	USA	PG	R	75	85	Ro	Ra	S	✔	✔	–	–	LR
14	Hoskinson *et al.* (2002)	UK	Sp	R	78	76	Ro	C&R	S	✔	✔	✔	✔	GEE
15	Farzaneh *et al.* (2004)	Canada	Sp	C	22	103	T	C&R	S	–	✔	✔	✔	LR
16	Gorni & Gagliani (2004)	Italy	PG	C	94	452	T	C&R	S	✔	✔	✔	✔	M-W
17	Çalişkan (2005)	Turkey	Sp	R	96	86	T	C&R	S	–	✔	✔	✔	χ^2

'–', missing information; UG, undergraduate students; PG, postgraduate students; Sp, specialist endodontists; R, retrospective study; C, prospective cohort study; RCT, randomized controlled trial; T, teeth; Ro, root; C&R, combined clinical and radiographic examination; Ra, radiographic examination only; S, strict criteria; L, loose criteria; LR, single level logistic regression; GEE, generalized estimating equations; χ^2, chi-square test; M-W, Mann–Whitney *U*-test.
[a]The treatments were carried out in Germany, Israel or USA by three different operators.

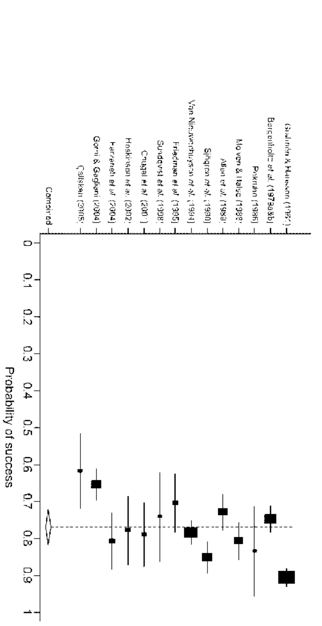

Figure 1 Probability of success based on strict radiographic criteria.

Qualification of operators (Undergraduate, postgraduate, specialist)
None of the reviewed studies had compared the outcome of 2°RCT by qualification of operators. The majority of the reviewed studies classified operator qualification as: undergraduate students (six studies), postgraduate students (two studies) or specialists (seven studies) (Table 2). The operators in the other two studies (Allen *et al.* 1989, Van Nieuwenhuysen *et al.* 1994) were a mixed group of dentists (undergraduate & postgraduate students, specialists) and a single dentist, respectively. From the pooled data, treatment carried out by specialists gave the lowest estimate of success, regardless of strict or loose criteria (Table 3). Meta-regression analysis, however, revealed that 'qualification of operator' had no significant influence on the outcome of 2°RCT on teeth with ($P = 0.6$) or without ($P = 0.2$) pre-operative lesion. The current data did not allow further stratified analyses by case complexity, thus the results should be interpreted with caution.

Success rates by clinical factors

Different studies have evaluated the influence of a range of different prognostic factors on outcome but the combinations of factors reported vary (Table 4).

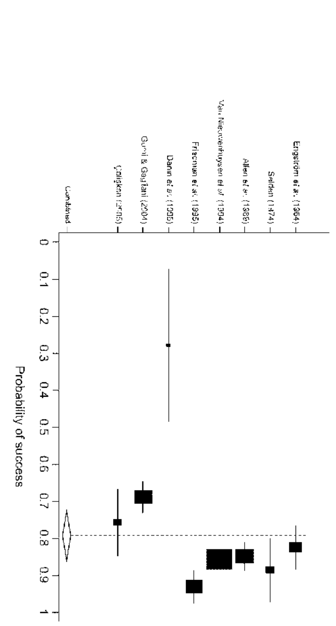

Figure 2 Probability of success based on loose radiographic criteria.

Table 3 Estimated success rates by study characteristics

Factor/categories	No. of studies identified[a]	Strict radiographic criteria: No. of studies	No. of units	Weighted pooled success rate (%)[b]	Loose radiographic criteria: No. of studies	No. of units	Weighted pooled success rate (%)[b]
Outcome measure used				76.7			77.2
Radiographic	3	2	311	80.1 (75.6, 84.5)	1	18	27.8 (7.1, 48.5)
Clinical + radiographic	14	12	3183	76.4 (70.9, 81.8)	7	1798	82.7 (76.5, 88.9)
Duration after treatment (months)							
6	1	0	–	–	1	155	94.2 (89.3, 97.3)
12	2	1	36	83.3 (67.1, 93.6)	1	18	27.8 (9.7, 53.5)
24	2	2	1008	70.0 (60.9, 79.2)	0	–	–
36	0	0	–	–	0	–	–
48	7	6	1082	85.5 (80.8, 90.1)	1	153	82.4 (75.4, 88.0)
>48	1	1	226	80.5 (74.8, 85.5)	0	–	–
Year of publication							
1960s	2	1	502	90.4 (87.9, 93.0)	1	153	82.4 (76.3, 88.4)
1970s	2	1	556	74.6 (71.0, 78.3)	1	52	88.5 (79.8, 97.1)
1980s	3	3	577	77.8 (71.3, 84.3)	1	315	84.8 (80.8, 88.7)
1990s	5	4	1057	77.9 (72.0, 83.9)	3	758	76.1 (62.0, 90.1)
2000s	5	5	802	72.7 (64.9, 80.5)	2	538	70.0 (66.2, 73.9)
Geographic location of study[c]							
N. American countries	5	4	503	74.7 (71.4, 78.1)	2	367	85.4 (81.8, 89.0)
Scandinavian countries	7	5	1601	81.5 (74.3, 88.7)	2	171	56.0 (2.5, 109.5)
Other countries	5	5	1390	72.9 (65.0, 80.9)	4	1278	80.9 (70.4, 91.5)
Qualification of operators							
Undergraduate students	6	5	1601	81.5 (74.3, 88.7)	1	153	81.0 (76.3, 88.4)
Postgraduate students	2	2	188	79.8 (74.1, 85.6)	0	–	–
Specialist	7	5	778	70.8 (64.0, 77.6)	5	736	73.2 (58.7, 87.7)

[a]Some of the studies identified for the respective factor provided success rates based on both strict and loose radiographic criteria.
[b]When data were available from only one study for a given factor, the success rate reported by that individual study is presented in this table.
[c]N. American countries = USA, Canada; Scandinavian countries = Norway, Sweden; Other countries = UK, Belgium, Italy, Saudi Arabia, Turkey.

Attempts to evaluate the effect of individual factors call for the pooling of various equivalent subsets of these studies. The results of the three approaches of analyses: (i) Intuitive synthesis of reported findings from individual studies; (ii) weighted pooled success rate by stratification of groups under each factor; and (iii) weighted effects (weighted pooled odds ratio) of these factors on success rates are presented in that order for each factor below. Considering only three studies had provided stratified data by clinical factors based on loose outcome criteria, *the quantitative analyses were only carried out on data based on strict criteria.*

Pre-operative factors

Gender. Only two ([1]Sjögren *et al.* 1990, Van Nieuwenhuysen *et al.* 1994) of the previous studies had investigated the influence of this factor but did not find any significant association between gender and success rate.

The above two studies did not provide the raw data for effect of gender; such data could however, be obtained from another study (Hoskinson *et al.* 2002) that had not analysed the data statistically (Table 5). The success rates for female patients were 44% higher than those for male patients. This result should be interpreted with caution because of the small sample size and substantially smaller number of male than female patients who had received 2°RCT in their study. Furthermore, all the treated teeth in the male patients were associated with a pre-operative periapical lesion whilst a smaller 70% of the teeth in the female patients were associated with a pre-operative lesion.

Age. Two studies ([2]Sjögren *et al.* 1990, Van Nieuwenhuysen *et al.* 1994) had analysed the influence of age on treatment outcome. The former

[1] Studies excluded from quantitative analyses for reasons given in Table 1.

Table 4 Clinical prognostic factors included in studies

Study ID	Author (Year)	Gender	Age	Health	Tooth type	Periapical status	Size of periapical lesion	Time interval before re-treatment	Pre-operative canal content	Pre-operative perforation	Pre-operative obstruction	Quality of pre-existing RF	Rubber dam isolation	Apical size of canal preparation	Taper of canal preparation	Separation of instrument	Irrigant	Medicament	Culture test	RF material technique	Sealer	Apical extent of RF	Quality of RF	No. of treatment visits	Restoration after 2RCT
1	Grahnén & Hanssen (1961)					✓											✓	✓		✓		✓		✓	
2	Engström et al. (1964)					✓	✓				☒						✓	✓	✓	✓		☒		✓	
3	Selden (1974)				☒	✓	✓																		
4	Bergenholtz et al. (1979a,b)				✓	✓	✓	✓					✓							✓		✓			
5	Pekruhn (1986)				☒								✓				✓	✓		✓	✓			✓	
6	Molven & Halse (1988)					✓														✓				✓	
7	Allen et al. (1989)				☒			☒	☒											✓					☒
8	Sjögren et al. (1990)	☒	☒		✓	✓	✓				☒		✓				✓		✓	✓		✓	✓	✓	☒
9	Van Nieuwenhuysen et al. (1994)	☒	☒				☒						☒				✓			✓	✓	☒	☒	☒	
10	Friedman et al. (1995)					✓											✓	✓		✓	✓	☒			☒
11	Danin et al. (1996)					✓	✓					✓	✓				✓	✓		✓				✓	
12	Sundqvist et al. (1998)					✓	☒	✓					✓				✓	✓	✓	✓		☒		✓	
13	Chugal et al. (2001)					☒	☒																		
14	Hoskinson et al. (2002)	✓	✓			✓	✓						✓	✓	✓		✓			✓	✓	✓	✓	✓	✓
15	Farzaneh et al. (2004)					✓		✓		✓		✓	✓				✓	✓		✓	✓	✓	☒	✓	✓
16	Gorni & Gagliani (2004)					✓			✓	✓	✓						✓	✓		✓					
17	Çalişkan (2005)			✓		✓	✓	✓	✓				✓				✓	✓		✓	✓			✓	
	Total no. of studies with raw data	1	1	1	2	13	7	4	2	2	1	2	8	1	1	0	12	9	3	15	6	5	2	10	2

RF, root filling; ✓, raw data available for estimation of pooled success rates or effects of the respective factor; —, the effect of the respective factor had been analysed statistically by individual study but raw data was not available for estimation of the effect in this review.

Table 5 Pooled weighted success rates by pre-operative clinical factors based on strict criteria

Factor	No. of studies	No. of cases	Weighted pooled success rate (%)[a]	Study ID[c]
Gender				
Female	1	56	89.2 (78.1, 96.0)	14
Male	1	20	45.0 (23.1, 68.5)	14
Age				
25–50 years	1	32	81.3 (63.6, 92.8)	14
>50 years	1	43	76.7 (61.4, 88.2)	14
Patient's health				
Healthy	1	86	61.6 (50.5, 71.9)	17
Unhealthy	No data	–	–	–
Tooth type				
Maxillary incisors/canines	2	108	62.6 (14.1, 111.2)	4, 8
Mandibular incisors/canines	2	49	59.1 (33.4, 84.8)	4, 8
Maxillary premolars	2	136	65.0 (31.3, 98.6)	4, 8
Mandibular premolars	2	89	71.8 (27.8, 115.9)	4, 8
Maxillary molars	2	49	68.0 (55.2, 80.9)	4, 8
Mandibular molars	2	70	85.0 (62.9, 107.1)	4, 8
Presence of periapical lesion				
Without Pa lesion	7(9)[b]	1117	93.5 (92.1, 95.0)	1, (2), 4, 6, 8, 10[d], 14–16
		1227	93.4 (91.6, 95.1)[d]	when #10 is included
With Pa lesion	10(13)[b]	1145	65.7 (58.6, 72.7)	1, (2), (3), 4, 6, 8, 10, (11), 12, 14–17
Size of periapical lesion				
Pa <5 mm	4(7)[b]	1386	67.3 (51.7, 83.0)	(2), 4, 8, (11), 14, 17
Pa >5 mm	4(7)[b]	875	41.7 (32.6, 50.8)	(2), (3), 4, 8, (11), 14, 17
Time interval between previous treatment and re-treatment				
≤1 year	1	17	70.6 (44.0, 89.7)	15
>1 year	4	452	66.2 (28.8, 83.7)	4, 12, 15, 17
Pre-operative canal content				
Gutta-percha	1	75	64.0 (52.1, 74.8)	17
Separated instrument	1	61	95.1 (86.3, 99.0)	16
Pre-operative perforation				
No	2	561	72.9 (40.3, 105.6)	15, 16
Yes	2	80	41.2 (30.5, 52.0)	15, 16
Pre-operative canal obstruction				
Calcification or presence of apical stop	1	103	66.0 (56.0, 75.1)	16
No obstruction	1	349	65.0 (59.8, 70.0)	16
Quality of pre-operative root fillings				
Satisfactory	1(2)[b]	19	68.4 (43.4, 87.4)	(11), 15
Unsatisfactory	1(2)[b]	80	87.5 (78.2, 93.8)	(11), 15

[a]Weighted pooled success rates were estimated using random effect model (where there was only one study, its reported success rate was presented).
[b]Number in bracket was the total number of studies using loose or strict radiographic criteria for determination of success.
[c]Study in bracket was not included in the estimation of pooled success rate because its outcome data for the given factor was based on loose radiographic criteria.
[d]Un-weighted pooled success rate was presented because 100% success rate for the associated category was reported by the respective study.

found no statistically significant difference in success rates stratified by age but the latter reported that the success rates reduced with increase in age.

Outcome data was only provided by one study (Hoskinson *et al.* 2002) (Table 5) and showed that treatments carried out in patients within the age band 25 50 years had a 4% higher chance of success than those carried out in older patients (>50 years). The results should again be interpreted with caution because of the small sample size.

General medical health. [2]Marending *et al.* (2005) had reported that conditions associated with impaired nonspecific immune responses reduced the success of root canal treatment. However, they did not stratify this analysis by 1°RCT or 2°RCT. Çalişkan (2005) reported that only healthy patients were included in their study. No further quantitative analyses were carried out due to absence of raw data for comparison.

Tooth type. Three studies ([2]Selden 1974, [2]Pekruhn 1986, Allen *et al.* 1989) had compared the outcome of treatment between tooth types. Only Allen *et al.* (1989) found statistically significant differences in success rates between tooth types. They reported that maxillary teeth were associated with a significantly higher success rate compared with mandibular teeth. This difference however was not significant when only molar teeth were included in the analysis.

The above three studies did not present raw outcome data by tooth type (maxillary incisor & canine, maxillary premolar, maxillary molar, mandibular incisor & canine, mandibular premolar, mandibular molar); such raw data *were* however provided by Bergenholtz *et al.* (1979a,b) and Sjögren *et al.* (1990). The weighted pooled success rates for mandibular molar teeth were the highest followed by those for mandibular premolar teeth and then maxillary premolar and molars and then incisors/canines (Table 5).

Periapical status. Five studies (Molven & Halse 1988, Friedman *et al.* 1995, [1]Chugal *et al.* 2001, Hoskinson *et al.* 2002, Gorni & Gagliani 2004) had compared the success rates of teeth/roots with or without periapical lesions, all found the former were associated with significantly lower success rates than the latter. Stratified outcome data were provided by thirteen studies (Table 4). The weighted pooled success rates for those without periapical lesion were 28% higher than for those with periapical lesion pre-operatively (Table 5).

Of the 13 studies providing data for estimation of pooled success rates by periapical status, 8 (Grahnén & Hanssen 1961, Engström *et al.* 1964, Bergenholtz *et al.* 1979a,b, Molven & Halse 1988, Sjögren *et al.* 1990, Hoskinson *et al.* 2002, Gorni & Gagliani 2004, Farzaneh *et al.* 2004) provided stratified outcome data by both teeth with and without periapical lesion for meta-analysis. It was evident that teeth without periapical lesion had 6.32 (95% CI: 4.04, 9.90) times higher odds of success than teeth with periapical lesions (Table 7a). The heterogeneity 16.3 (7 df) was substantial (Table 7a) and could be partly explained by the 'decade of publication' and 'duration after treatment' when investigated using meta-regression models (*results not shown*).

Size of periapical lesion. Seven studies had statistically compared the success rates of teeth with pre-operative, large or small periapical lesions; four (Bergenholtz *et al.* 1979a,b, Van Nieuwenhuysen *et al.* 1994, Sundqvist *et al.* 1998, [1]Chugal *et al.* 2001) found that teeth with smaller lesions were associated with significantly higher success rates than those with larger lesions. In contrast, Sjögren *et al.* (1990), Danin *et al.* (1996) and Çalişkan (2005) found no statistical difference.

Seven reviewed studies (Table 4) provided outcome data by the size of lesion. By pooling the data for lesion size into <5 mm or ≥5 mm in diameter, the weighted pooled success rate for small lesions was 25% higher than that for large lesions (Table 5). The estimated pooled odds of success for small lesions was significantly higher when compared to the pooled odds of success for large lesions (OR = 2.64; 95% CI: 1.67, 4.17) (Table 7b). Selden (1974) was excluded from the meta-analysis because all the cases with small lesion were successful. Although, the heterogeneity 7.0 (5 df, $P = 0.224$) in the estimate was not significant, it could partly be explained by the 'duration after treatment'. In addition, the effect of the size of lesion only reached the 10% significance level when the covariate 'duration after treatment' was entered simultaneously into the meta-analysis regression model.

Time interval between 1°RCT and 2°RCT. Only two studies ([2]Allen *et al.* 1989, Farzaneh *et al.* 2004) had investigated the effect of this factor on outcome and both found no significant association. Three other studies had only included teeth receiving 1°RCT at least 2 years (Bergenholtz *et al.* 1979a,b, Çalişkan 2005) or 4 5 years (Sundqvist *et al.* 1998) previously. By pooling the data for time interval between 1°RCT and 2°RCT into ≤1 year or >1 year, the difference in weighted pooled success rates was 5% in favour of those cases with previous root canal treatments (1°RCT) of ≤1 year duration. No further meta-analysis was carried out due to insufficient data.

Pre-operative canal content. The success rates of 2°RCT related to the presence of different pre-operative foreign materials in the root canal system had only been investigated by [2]Allen *et al.* (1989) but they included data from surgical re-treatment

[2]1°RCT cases were included in the stratified data by potential influencing factors.

cases (54% of the samples) in the analysis. They found that teeth with 'cement' root filling pre-operatively were associated with significantly lower success rates than those teeth with 'gutta-percha' or 'silver point' root fillings pre-operatively. Stratified outcome data by teeth with pre-operative gutta-percha root fillings or presence of separated instrument were given by Çalişkan (2005) and Gorni & Gagliani (2004), respectively (Table 5). No further meta-analysis was carried out due to insufficient data.

Procedural errors in previous canal preparation (1°RCT). The procedural errors investigated had included: canal perforation, obstruction and 'root canal morphology alteration by previous treatment' which was defined by Gorni & Gagliani (2004) as presence of transportation, perforation, stripping or internal resorption, the last condition was, however not related to the previous treatment (1°RCT).

Only one study (Farzaneh *et al.* 2004) had investigated the effect of pre-existing perforation on outcome; the success rates were significantly reduced by the presence of this procedural error. However, [1]Main *et al.* (2004) reported the periradicular radiolucency associated with the perforations were completely resolved in all cases with pre-existing perforation. Success rates stratified by this factor were provided by two studies (Farzaneh *et al.* 2004, Gorni & Gagliani 2004); the weighted pooled success rate for teeth without pre-operative perforation was 32% higher than that for teeth with pre-operative perforation (Table 5).

Four studies had investigated the effects of pre-operative canal obstruction ([1]Strindberg 1956, [2]Engström *et al.* 1964, Sjögren *et al.* 1990, Gorni & Gagliani 2004). The former two studies found that teeth with canals inaccessible towards the apex were associated with significantly lower success rates, whereas the latter two studies did not find any significant association. Sjögren *et al.* (1990) declared that they could not make any distinction between canals obliterated by denticles, tertiary dentine and/or obturations caused by improper previous (1°RCT) instrumentation and had not presented stratified outcome data for this factor. The stratified success rates *were* however, provided by Gorni & Gagliani (2004) (Table 5) but no further meta-analysis was carried out due to insufficient data.

Quality of pre-operative root fillings. Two studies (Danin *et al.* 1996, Farzaneh *et al.* 2004) have compared the success rates of 2°RCT on teeth with satisfactory versus unsatisfactory pre-existing root fillings (1°RCT). The former did not find any significant influence by the apical extent of pre-existing root filling but the latter found the success rates for those teeth with adequate pre-operative root fillings (extended to 0 2 mm from the radiographic root end with no voids) were significantly lower than those for teeth with inadequate pre-operative root fillings, in the case for teeth with pre-operative periapical lesions. The outcome data by this factor from Farzaneh *et al.* (2004) is presented in Table 5.

Intra-operative factors

Use of rubber dam isolation during treatment. Eight studies (Table 4) reported the routine use of rubber dam during treatment whilst nine studies did not mention the use of rubber dam isolation in their treatment protocol. One study (Van Nieuwenhuysen *et al.* 1994) had compared the outcome of 2°RCT using rubber dam versus cotton roll isolation. They found the use of the former was associated with significantly higher success rates but the requisite raw data were not available. The weighted pooled success rates of treatment using rubber dam isolation in those studies ($n = 7$) was 77.1%, based on strict criteria (Table 6). There was insufficient data for further analysis.

Apical extent of instrumentation. Only one study (Bergenholtz *et al.* 1979a) had investigated the effect of this factor (Table 4). It had been dichotomized into instrumentation beyond the apex or not: instrumentation beyond the apex was deemed a cleaned apex. The former cases (56%) were associated with significantly lower success rate than the latter cases (88%), regardless of the pre-operative periapical status of teeth (Table 6). They pointed out that the majority of failures occurring amongst 'clean roots' were complicated by overfilling during 2°RCT. No further meta-analysis was carried out due to insufficient data.

Apical size of canal preparation. Three previous studies ([1]Strindberg 1956, [1]Kerekes & Tronstad 1979, Hoskinson *et al.* 2002) (Table 4) had analysed the effect of apical size of canal preparation on treatment outcome: they found no significant association. Their analyses were however, not stratified by 1°RCT and 2°RCT and only a small proportion of re-treatment cases (30%, 9%, 16%, respectively) were included in their studies. The raw data for 2°RCT from the study by

Table 6 Pooled weighted success rates by intra-& post-operative clinical factors

Factor	No. of studies	No. of cases	Weighted pooled success rate (%)[a]	Study ID[c]
Use of rubber dam isolation				
Yes	7(8)[b]	1174	77.1 (71.6, 82.7)	4, 5, 8, (11), 12, 14, 15, 17
No	No data	–	–	–
Instrumentation beyond apex				
Yes	1	228	55.7 (49.3, 62.1)	4
No	1	328	87.8 (84.3, 91.3)	4
Apical size of canal preparation (ISO size)				
≤30	1	58	84.5 (75.2, 93.8)	14
>30	1	18	55.6 (32.6, 78.5)	14
Taper of canal preparation				
0.05	1	44	79.5 (67.6, 91.5)	14
0.10	1	32	75.0 (60.0, 90.0)	14
Type of irrigant				
NaOCl	8(10)[b]	1198	74.7 (67.6, 81.8)	(2), 5, 8, 10, (11), 12, 14–17
H_2SO_4	1	502	90.4 (87.9, 93.0)	1
NaOCl & EDTA	1	612	78.3 (75.0, 81.5)	9
Type of medicament				
$Ca(OH)_2$	5(6)[b]	792	69.1 (63.8, 74.4)	10, (11), 12, 14, 16, 17
Iodine	0(1)[b]	–	–	(2)
Creosote	1	502	90.4 (87.9, 93.0)	1
None	1	36	83.3 (71.2, 95.5)	5
Culture results prior to obturation				
Negative culture	2(3)[b]	392	84.4 (80.4, 88.4)	(2), 8, 12
Positive culture	1(2)[b]	16	27.0 (4.3, 77.7)	(2), 12
Negative culture – no pa	0(1)[b]	–	–	(2)
Positive culture – no pa	0(1)[b]	–	–	(2)
Negative culture – pa	1(2)[b]	44	79.5 (67.6, 91.5)	(2), 12
Positive culture – pa	1(2)[b]	6	33.3 (4.3, 77.7)	(2), 12
Root filling material/technique				
Gutta-percha with sealer	8	1808	73.5 (68.5, 78.4)	5, 7, 9, 10, 14–17
Kloropercha	5(7)[b]	1601	81.5 (74.3, 88.7)	1, (2), 4, 6, 8, (11), 12
Type of sealer				
Zinc oxide eugenol based	4	1176	75.4 (66.8, 83.9)	5, 9, 14, 15
Glass ionomer based (Ketac Endo®)	1	128	70.3 (62.4, 78.2)	10
Polyvinyl resin based (Diaket®)	1	86	61.6 (51.4, 71.9)	17
Apical extent of root filling				
Short-filled	3	229	87.4 (74.2, 100.7)	1, 8, 14
Flush-filled	4	310	80.5 (68.6, 92.4)	1, 8, 14, 15
Long-filled	4	406	63.1 (42.9, 83.4)	1, 4, 8, 14
Short-fill – no pa	2	159	100.0	1, 14
Flush-fill – no pa	2	120	97.2 (94.3, 100.1)	1, 14
Long-fill – no pa	2(3)[d]	179	84.0 (78.8, 89.1)	1, 4, [d]14
		194	84.0 (78.8, 89.3)[d]	When #14 included
Short-fill – pa	3	70	78.5 (69.0, 88.0)	1, 8, 14
Flush-fill – pa	3	112	72.2 (64.0, 80.4)	1, 8, 14
Long-fill – pa	4	212	54.2 (30.8, 77.6)	1, 4, 8, 14
Quality of root filling				
Satisfactory	2	157	71.8 (64.8, 8.8)	8, 14
Unsatisfactory	1(2)[d]	13	30.8 (5.68, 55.9)	8, 14[d]
		15	26.6 (4.3, 49.0)[d]	When #14 was included
Number of treatment visits				
Single visit	1(2)[d]	52	83.3 (71.2, 95.5)	5, 15[d]
			86.1 (27.7, 144.4)[d]	When #15 was included
Multiple visits	7(9)[b]	1461	79.5 (73.2, 85.8)	1, (2), 6, 8, (11), 12, 14, 15, 17
Quality of restoration				
Satisfactory	2	155	84.1 (78.4, 89.9)	14, 15

Table 6 (Continued)

Factor	No. of studies	No. of cases	Weighted pooled success rate (%)[a]	Study ID[c]
Unsatisfactory	2	20	60.0 (38.6, 81.5)	14, 15

[a] Weighted pooled success rates were estimated using random effect model (where there was only one study, its reported success rate was presented).
[b] Number in bracket was the total number of studies using loose or strict radiographic criteria for determination of success.
[c] Study in bracket was not included in the estimation of pooled success rate because its outcome data for the given factor was based on loose radiographic criteria.
[d] Study excluded for estimation of the weighted pooled success rate because the success rate for the associated category was 100% or 0%.

Hoskinson *et al.* (2002) (Table 4) showed that the success rate for small (size 20–30) apical preparations (85%) was higher than that for large (size 35 90) apical preparations (56%) (Table 6). The effect of size of preparation could not be analysed further due to insufficient data.

Taper of canal preparation. Only one study (Hoskinson *et al.* 2002) (Table 4) analysed the influence of canal preparation taper on 2°RCT; they did not find any significant difference in success rate between 0.05 and 0.10 canal tapers. However, the result of their analysis might have been confounded by the concomitant change in the concentration of the sodium hypochlorite irrigant and the root filling technique. The success rates stratified by taper of canal preparation are presented in Table 6. The effect of taper of canal preparation could not be analysed further due to insufficient data.

Separation of instrument during 2°RCT. [1]Strindberg (1956) found that instrument separation during 2°RCT reduced the success rate significantly. None of the studies selected had stratified outcome data for this factor.

Irrigant. Different types of irrigants have been used singly or in various combinations in the studies

Table 7 Summary of meta-analyses for the effects of clinical factors on success rates of 2°RCT

Comparisons	No. of studies	Odds ratio	95% CI	Heterogeneity χ^2-value	Heterogeneity P-value
(a) Effects of presence of pre-operative periapical lesion					
Present	8	1	–	–	–
Absent		6.32	4.04, 9.90	16.3	0.022
(b) Effects of size of pre-operative lesion					
Large radiolucency	6	1	–	–	–
Small radiolucency		2.64	1.67, 4.17	7.0	0.224
(c) Effects of pre-obturation culture results					
+ve culture result	2	1	–	–	–
−ve culture result		4.30	0.34, 54.9	6.9	0.009
(d) Effects of pre-obturation culture results (teeth with pre-operative periapical lesion)					
+ve culture result	2	1	–	–	–
−ve culture result		4.81	0.72, 32.23	3.4	0.066
(e) Effects of apical extent of root filling					
Long	3	1	–	–	–
Flush		2.36	1.36, 4.10	1.4	0.500
Short		4.11	2.10, 8.07	2.5	0.286
(f) Effects of apical extent of root filling (teeth with pre-operative lesion)					
Long	3	1	–	–	–
Flush		1.65	0.86, 3.16	0.39	0.824
Short		1.72	0.81, 3.64	1.17	0.558
(g) Effects of quality of coronal restoration					
Unsatisfactory	2	1	–	–	–
Satisfactory		3.31	1.07, 10.3	0.21	0.647

reviewed, including solutions of: sodium hypochlorite (n = 10 studies), sulphuric acid (50%) or sodium bicarbonate (Grahnén & Hanssen 1961); a combination of sodium hypochlorite, ethylene-diamine-tetra-acetic acid (EDTA) solution and urea peroxide has also been utilized (Van Nieuwenhuysen *et al.* 1994). Some studies (five studies) did not present this information. None of the studies had systematically investigated the effect of irrigant on success rates. The weighted pooled success rates by different types of irrigant are presented in Table 6. The effect of this factor could not be analysed further due to insufficient data.

Medicament. Some studies standardized the type of medicaments used, and included: calcium hydroxide (n = 6), creosote (n = 1) and iodine (n = 1). In contrast, Sjögren *et al.* (1990) reported the use of calcium hydroxide in most cases but potassium iodide and camphorated phenol were sometimes used. Whilst, Van Nieuwenhuysen *et al.* (1994) reported the use of paraformaldehyde in the early part of their study, replaced later by calcium hydroxide. No inter-appointment medicament was used by Pekruhn (1986) because all the cases were completed in one visit. Six studies did not provide this information.

The pooled success rates stratified by different types of medicament are presented in Table 6. There were no data on success rates of treatment using iodine, based on strict criteria. Interestingly, the pooled success rate of 2°RCT using $Ca(OH)_2$ (68.2%) was much lower than that using creosote (90.4%) as the inter-appointment medicament. Although the data for creosote originated from a single study (Grahnén & Hanssen 1961), the total number of cases treated using $Ca(OH)_2$ in the pooled data (n = 792) was comparable to the number treated with creosote (n = 502). It is worthy of note that the majority (76%) of the roots in the creosote data were not associated with a pre-operative periapical lesion. No further meta-analysis was carried out due to insufficient data.

Root canal bacterial culture test results (positive or negative) prior to obturation Comparison of pre-obturation root canal culture test results for any periapical status. Two studies (Engström *et al.* 1964, Sundqvist *et al.* 1998) had investigated the influence of pre-obturation bacterial culture results on outcome of 2°RCT and found that canals with negative culture results prior to obturation were associated with significantly higher success rates than those with positive culture results. In one study (Sjögren *et al.* 1990), the teeth were root filled only when a negative bacterial culture result was obtained.

The pooled weighted success rates for teeth with negative culture results were higher than those with positive culture results by 57% (Table 6). The meta-analyses showed the odds of success of teeth with pre-obturation negative culture were higher than those of teeth with a positive culture (OR = 4.3; 95% CI: 0.3, 55.0) but the difference was not statistically significant (Table 7). Although the heterogeneity [6.9 (1 df)] was significant (P = 0.009), further meta-regression analysis was not carried out because of insufficient data.

Comparison of pre-obturation root canal culture test results for teeth without periapical lesion. For those teeth without a pre-operative periapical lesion (data provided by Engström *et al.* 1964), the success rate for teeth with negative culture results was 9% higher than for those teeth with positive cultures. However, their data was based on loose criteria and was therefore not presented in Table 6. The effect was not estimated because of insufficient data.

Comparison of pre-obturation root canal culture test results for teeth with periapical lesions. Sundqvist *et al.* (1998) found that culture results had a significant influence on outcome of re-treatment on teeth associated with periapical lesions. For those teeth with pre-operative periapical lesions, the success rates reported by Sundqvist *et al.* (1998) for teeth with negative bacterial cultures prior to root filling were 46% higher than those for teeth with positive cultures (Table 6). The effect estimated using meta-analysis was not statistically significant (OR = 4.8; 95% CI: 0.72, 32.2) with substantial heterogeneity 3.4 (df = 1, P = 0.066) but no further meta-regression was carried out due to insufficient data (Table 7d).

Root filling material and technique. The types of root filling materials reported were gutta-percha with various types of sealer (n = 8) or gutta-percha softened in chloroform (n = 7), but three studies did not provide such information. Of the eight studies using gutta-percha and sealer, only three studies (Pekruhn 1986, Gorni & Gagliani 2004, Çalişkan 2005) standardized the obturation technique. The former two used warm vertical compaction technique whilst Çalişkan (2005) used cold lateral compaction technique. Four studies (Van Nieuwenhuysen *et al.* 1994, Friedman *et al.* 1995, Hoskinson *et al.* 2002, Farzaneh *et al.* 2004) did not standardize the root filling technique and one (Allen *et al.* 1989) did not provide such information. Van Nieuwenhuysen *et al.* (1994) found the use of lateral compaction technique was associated with significantly higher success rate than the use of a single cone technique, in contrast to [1]Strindberg (1956) and [2]Friedman *et al.* (1995) who did not find any significant influence of root filling technique on success rates. The pooled success rate for teeth root filled with gutta-percha and sealer was 7% lower than for those filled with gutta-percha softened in chloroform (Table 6). The effects of root filling techniques and materials were not estimated due to insufficient data.

Three types of sealer have been used, including: Zinc oxide eugenol based sealers (4 studies), glass ionomer based sealers (KetacEndo®; ESPE Gmbh, Seefeld, Germany) (1 study) or resin based sealer (Diaket®; ESPE Gmbh, Seefeld, Germany) (one study). Eleven studies did not provide such information (Table 4). None of the previous studies had investigated the effect of sealer on the outcome of 2°RCT. The pooled success rates for teeth filled with the resin based sealer (62%) was lower than those obturated with zinc oxide eugenol based (75%) or glass ionomer based (70%) sealers (Table 6). The effect of type of sealers was not investigated further due to insufficient data.

Apical extent of root filling. Nine studies ([2]Grahnén & Hanssen 1961, [2]Engström *et al.* 1964, Bergenholtz *et al.* 1979a,b, Sjögren *et al.* 1990, Van Nieuwenhuysen *et al.* 1994, [2]Friedman *et al.* 1995, Sundqvist *et al.* 1998, [2]Hoskinson *et al.* 2002, Farzaneh *et al.* 2004) had investigated the influence of apical extent of root filling on treatment outcome statistically. They classified the various extents into three categories for statistical analyses: >2 mm short of radiographic apex (short), within 0 2 mm of the radiographic apex (flush) and extruded beyond the radiographic apex (long). Five studies ([2]Grahnén & Hanssen 1961, [2]Engström *et al.* 1964, Bergenholtz *et al.* 1979a,b, Van Nieuwenhuysen *et al.* 1994, [2]Friedman *et al.* 1995) found that this factor had significant influence on the success rates; long root fillings were associated with the lowest success rates ([2]Grahnén & Hanssen 1961, [2]Engström *et al.* 1964, Bergenholtz *et al.* 1979a,b) whilst flush root fillings were associated with the highest success rates ([2]Friedman *et al.* 1995, Farzaneh *et al.* 2004). The pooled success rates by apical extent of root fillings in descending order were: short (87%), flush (81%) and long (63%) root fillings but worse in the presence of a periapical lesion (Table 6). The rank order remained the same regardless of the periapical status.

Some studies provided the success rates stratified by periapical status and apical extent of root filling. Sjögren *et al.* (1990) found the apical extent of root filling did not influence the outcome of 2°RCT on teeth with periapical lesions. The pooled success rates for long root fillings were the lowest regardless of the periapical status (Table 6).

Only three studies presented success rates by all three extents (short, flush, long) of root filling for meta-analyses. Teeth with short (OR = 4.11; 95% CI: 2.10, 8.07) or flush (OR = 2.36; 95% CI: 1.36, 4.10) root fillings had significantly higher success rates than those with long root fillings (Table 7c). The results of meta-analyses on the data from teeth with pre-operative periapical lesions revealed similar trends with lower odds ratios and statistically insignificant findings (Table 7f). The heterogeneity was not significant, therefore further meta-regression analysis was not performed.

Quality of root filling. Out of the four studies (Table 4) which had analysed this aspect statistically, three (Sjögren *et al.* 1990, Van Nieuwenhuysen *et al.* 1994, Farzaneh *et al.* 2004) found that teeth with satisfactory root fillings were associated with significantly higher success rates than those with unsatisfactory root fillings. Satisfactory root fillings had been defined as 'adequate seal', 'good apical seal', 'absence of voids', whilst Van Nieuwenhuysen *et al.* (1994) also considered the apical extent of root fillings.

Only two studies provided stratified data by quality of root filling. The pooled success rate for teeth with satisfactory root fillings was 41% higher than for those teeth with unsatisfactory root fillings (Table 6). There were, however no successful cases with unsatisfactory root filling in one study (Hoskinson *et al.* 2002), therefore no further meta-analysis was carried out due to insufficient data.

Number of treatment visits. Five studies completed treatment in either one or multiple visits, eight studies carried out treatments over multiple visits only, only one study completed all treatment in one visit, whereas others (three studies) did not provide this information. Two studies (Van Nieuwenhuysen *et al.* 1994, Farzaneh *et al.* 2004) compared the outcome of treatment carried out over single or multiple visits, the former found the outcome of 2°RCT was significantly improved by multiple visit treatment and better still if the canal preparation and disinfection were completed in the first visit. In contrast, the latter study did not find any significant difference. The pooled success rate for single-visit treatment was 4.8% higher than the success rate for multiple-visit treatment but only one study had contributed to the data based on strict criteria for single-visit treatment (Table 6). The effect of number of treatment visits was not estimated due to insufficient data.

Type and quality of coronal restoration after 2°RCT. Five studies had analysed the influence of type or quality of coronal restoration on treatment outcome. Different comparisons had been made: restored versus unrestored teeth ([2]Friedman *et al.* 1995), permanent versus temporary restorations (Allen *et al.* 1989, [2]Friedman *et al.* 1995, Farzaneh *et al.* 2004), crown versus plastic restorations (Sjögren *et al.* 1990, [2]Friedman *et al.* 1995), presence versus absence of post ([2]Friedman *et al.* 1995), nonabutment versus abutment (Sjögren *et al.* 1990) and satisfactory versus unsatisfactory restorations ([2]Hoskinson *et al.* 2002). Hoskinson *et al.* (2002) defined satisfactory restorations as those with no evidence of marginal discrepancy, discolouration or recurrent caries at the restoration margin with no history of decementation. Teeth that had been restored or permanently restored were associated with significantly higher success rates than their contrary counterpart (Allen *et al.* 1989, [2]Friedman *et al.* 1995, Farzaneh *et al.* 2004). The type of restoration (Sjögren *et al.* 1990, [2]Friedman *et al.* 1995) was found to have no significant influence on the outcome of 2°RCT. Stratified data were provided by two studies (Hoskinson *et al.* 2002, Farzaneh *et al.* 2004) (Table 4) and the pooled success rate for teeth with satisfactory restorations was 24% higher than for those with unsatisfactory restorations (Table 6). The effect of quality of coronal restoration (OR = 3.31; 95% CI: 1.07, 10.3) was estimated based on the data from these two studies and found to be significant at the 5% level (Table 7g). The heterogeneity was not significant therefore further meta-regression analysis was not carried out.

Discussion

The number of clinical outcome studies on 2°RCT (n = 40 upto end of 2006) identified for this review was much smaller than those on 1°RCT (n = 119 upto end of 2003) (Ng *et al.* 2007). It was also noted that half of the articles on 2°RCT were published in the 1990s and 2000s whilst the number of those on 1°RCT were more evenly distributed amongst the different decades since 1960. This difference may reflect the general increase in awareness of dental health, tooth preservation and expansion in availability of aids and techniques to facilitate nonsurgical root canal re-treatment (Carr 1992). From 1992 to 2002, the number of surgical re-treatments carried out within the National Health Service in UK was reduced by one-third and this figure has continued to decline in recent years (Dental Practice Board 2005).

Most of the selected studies were prospective cohort or retrospective studies, therefore the levels of evidence provided were rated as Grade B (levels 2 or 3) based on the criteria given by the Oxford Centre for Evidence-Based Medicine (Phillips *et al.* 1998). This level of evidence was similar to the quality of 1°RCT outcome studies (Ng *et al.* 2007). The literature search identified two randomized controlled trials (Danin *et al.* 1996, Kvist & Reit 1999) comparing the outcome of surgical versus nonsurgical re-treatment and their data were analysed in a recently published Cochrane review (Del Fabbro *et al.* 2007). The study by Kvist & Reit (1999) was excluded from the present quantitative analysis because the overall success rates could not be calculated from the data presented in their paper. Nevertheless, both studies reported that surgical re-treatment was associated with higher success rates than 2°RCT, at 1-year after treatment, although in both studies the differences were not significant. Danin *et al.* (1996) probably could not reach significance because of the small sample size (18–19 patients per group) and Kvist & Reit (1999) failed to show any difference in the outcome at four-years post-operatively. The latter group hypothesized that surgical re-treatment resulted in more rapid initial bone fill but were associated with a higher risk of 'late failures'. No randomized controlled trial has thus far investigated any aspect of 2°RCT procedures.

The substantial variations and short-comings in the design amongst studies on outcome of 2°RCT were similar to those on 1°RCT (Ng *et al.* 2007). However, the median recall rate reported by studies on 2°RCT (74%) was substantially higher than that reported in studies on 1°RCT (53%). The implications of recall rate on the results from outcome studies were fully discussed previously (Ng *et al.* 2007); the same arguments apply here. The employment of at least two radiographic observers was another 'good practice' more frequently employed in 2°RCT outcome studies compared to 1°RCT (76% vs. 14%). Specialists were more frequently employed as operators in 2°RCT studies (41%) than in 1°RCT studies (37%). The pooled success rate for 2°RCT performed by specialists was however lower than when performed by undergraduate or postgraduate students. In contrast, 1°RCT carried out by postgraduate students and specialists had the higher pooled success rates than that performed by undergraduate students (Ng *et al.* 2007). This discrepancy may possibly be attributable to specialists managing more complex biological or technical problems, perhaps involving perforations, blockages, separated instruments or persistent infections. As the studies did not report on these factors, this supposition could not be tested in the meta-analysis.

The weighted pooled success rates from the 17 studies reviewed were 76.7% and 77.2% based on strict or loose criteria for success, respectively. The negligible difference in the weighted pooled success rates determined by loose and strict criteria for 2°RCT in this review was unexpected and was in contrast to the findings for 1°RCT (Ng *et al.* 2007). The difference could be attributable to the substantially smaller number of studies contributing to the outcome data based on loose ($n = 8$) compared to strict ($n = 14$) criteria and a possible outlier (Danin *et al.* 1996) in the pool (Fig. 2). The sample size in the latter was small ($n = 18$) with the lowest reported success rate (28%) based on 'loose' criteria compared with other studies (69 93%). After excluding Danin *et al.* (1996), the pooled success rate for loose criteria was found to increase to 83% (95% CI: 77%, 89%), 7% higher than the weighted pooled success rate based on strict criteria. This difference was slightly lower than that for 1°RCT (Ng *et al.* 2007). The slightly higher weighted pooled success rate based on strict criteria for 2°RCT (77%, 14 studies) compared to 1°RCT (74%, 40 studies) (Ng *et al.* 2007) was also unexpected. This finding contradicts the commonly held belief (Selden 1974, Pekruhn 1986, Sjögren *et al.* 1990, Friedman *et al.* 1995) that 1°RCT is associated with better outcome than 2°RCT due to the difference in the nature (Gulabivala 2004) and location of root canal infection (Nair *et al.* 2005).

Eight of the studies had presented stratified outcome data for 1°RCT and 2°RCT, of which seven had presented data based on strict criteria. However, the relative proportion of roots/teeth which had 2°RCT versus 1°RCT included in these studies were low and ranged from 4% to 51%. This may have rendered the statistical comparison under-power which is apparent in the meta-analysis comparing 1° and 2°RCT (Fig. 3); it shows that 1°RCT was associated with higher odds of success (OR = 1.26; 95% CI: 0.77, 2.07) but the difference was not significant ($P = 0.365$) (Fig. 3). A further meta-analysis was carried out on the data from teeth with pre-operative lesions in four studies (Grahnén & Hanssen 1961, Selden 1974, Sjögren *et al.* 1990, Hoskinson *et al.* 2002), which revealed the odds ratio increased to 1.63 (95% CI: 0.75, 3.55) but the

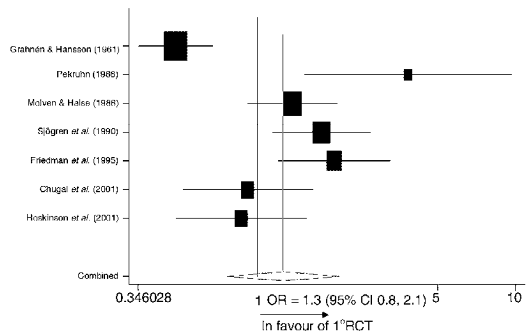

Figure 3 Comparison of the odds of success of 1°RCT and 2°RCT.

result was not statistically significant at the 5% level. It could be concluded that the differences in success rate between 1°RCT and 2°RCT are clinically genuine but there was insufficient statistical power (only four studies, $n = 999$ units for 1°RCT and $n = 309$ units for 2°RCT) to prove a significant difference. Further well designed prospective cohort studies are therefore required to confirm this relationship.

Given the small number of studies that could be included in this review, the meta-analyses on the effects of several prognostic factors could be considered to be compromised by the lack of statistical power to demonstrate a significant influence. Alternatively, the lack of power may have potentially over-estimated the magnitude of effect. The adoption of the previously used process of 'triangulation' of different analytical approaches (Ng *et al.* 2007, 2008) to draw meaningful conclusions would therefore seem sensible. Of the prognostic factors investigated, pre-operative presence and size of periapical lesion followed by apical extent of root fillings were the most frequently and thoroughly investigated. The observations were similar to those based on data for 1°RCT (Ng *et al.* 2008). Other pre-operative factors specifically relevant to 2°RCT (time interval between 1°RCT and 2°RCT, quality of pre-existing root filling, pre-existing canal content, root perforation, root canal obstruction) were poorly investigated. The deficiency in the data on intra-operative factors was more severe for 2°RCT than for 1°RCT (Ng *et al.* 2008) outcome studies.

On the influence of the periapical status on 2°RCT outcome, all three analytical approaches concurred and demonstrated a significantly higher (28%, OR = 6.3) success rate for teeth without periapical lesions compared with those with periapical lesions. The difference was larger than between such groups undergoing 1°RCT (10% difference in success rates, OR = 2.0) (Ng *et al.* 2008). The odds ratios for 2°RCT may have been over-estimated in the present review due to the small number of studies and the small sample size in the studies on 2°RCT. If the result is true, the greater impact of periapical status on 2°RCT may support the hypothesis that the infection in root-treated teeth with persistent periapical lesions could be more resistant to treatment (Gulabivala 2004). Alternatively, the problem may be one of inaccessible location of the infection within the root canal system, due to natural (Wada *et al.* 1998, Nair 2004, Nair *et al.* 2005) or iatrogenic (Seltzer *et al.* 1967) impediments. Although the success rates of 2°RCT on teeth with smaller lesions was significantly higher (25%, OR = 2.7) than for those with larger lesions, the difference failed to reach a statistically significant level (5%) when the covariate 'duration after treatment' was simultaneously entered into the meta-analysis regression model. The statistical heterogeneity could also be partly explained by the 'duration after treatment', consistent with the results of the systematic review on 1°RCT (Ng *et al.* 2008). It may therefore be concluded that larger lesions take longer to heal completely after 2°RCT, highlighting the importance of considering the confounder 'duration after treatment' when investigating the effect of prognostic factors.

Although the influence of bacterial culture results on the outcome of 2°RCT has only been investigated by two studies, the present review found a large but insignificant difference (32%, OR = 4.3) in success rates between those teeth with negative culture and those with positive culture. The difference was reduced slightly (46%) when only teeth with pre-operative lesion were included in the analysis. It may be hypothesized that the lack of significance was attributable to the small sample size since the bacterial culture results had a genuine negative impact on success of 2°RCT. The magnitude of impact of this factor on 2°RCT appeared to be much higher than on 1°RCT (Ng *et al.* 2008); this may again be due to over-estimation of the results because of the small sample size. Speculating that the result is true, the observation may be explained by difference in the nature of the residual bacteria present (Gulabivala 2004).

The intuitive (nine studies) and quantitative (three studies) analyses on the effects of the apical extent of root filling on 2°RCT gave somewhat different perspectives. These differences could be attributed to the substantial discrepancy in the number of studies contributing to the two analyses. The effect of this factor on 2°RCT outcome was profound and similar to its effect on 1°RCT (Ng *et al.* 2008). Teeth with long root fillings were associated with significantly lower pooled weighted success rates when compared with teeth with flush or short root fillings. Furthermore, for teeth with pre-operative periapical lesions, short root fillings were associated with higher success rates than flush root fillings, although the difference was small (7%) and statistically insignificant (OR = 0.84, 95% CI: 0.41, 1.72); this outcome was in contrast to the findings for 1°RCT (Ng *et al.* 2008). This finding was particularly unexpected because short root fillings could also be taken as a surrogate measure for inadequate cleaning of the apical canal terminus. This circumstance could be precipitated by either natural (calcification) or iatrogenic (pulpo-dentinal debris, foreign materials) obstructions. Previous reports on the effect of canal obstructions on the outcome of 1°RCT and 2°RCT have been contradictory and confusing ([1]Strindberg 1956, [2]Engström *et al.* 1964, Sjögren *et al.* 1990). The former two studies did not stratify their analyses by the two types of treatment and reported a significant influence from canal obstruction. In contrast, Sjögren *et al.* (1990) reported that the level of instrumentation as well as the apical extent of root fillings had no significant influence on the outcome of 2°RCT on teeth with apical periodontitis. To further accentuate the contrast, the same study (Sjögren *et al.* 1990) found a significant influence of canal obstruction on the outcome of teeth with apical periodontitis undergoing 1°RCT. The authors stressed that all cases with short root fillings and pre-operative periapical lesions were classified amongst those that could not be instrumented to their full length. Close inspection of their data revealed that 2°RCT teeth with pre-operative periapical lesions and long root fillings (50% of 26 roots) were associated with 15–17% lower success rate compared with those teeth with flush (0 2 mm short of radiographic apex) (67% of 51 roots) or short (≤2 mm short of radiographic apex) (65% of 17 roots) root fillings. The lack of statistical significance in the reported difference may again be due to insufficient sample size. The lack of difference in success rate between teeth with flush and short root fillings was also unexpected. The success rates for the 2°RCT (65%) and 1°RCT (68%) on teeth with pre-operative periapical lesions with short root fillings were similar. It could therefore be inferred that 'short' root fillings had the same effect on the outcome of both types of treatment. In contrast, the 2°RCT cases with flush root fillings (67%) were associated with a much lower (27%) success rate than their 1°RCT (94%) counterparts. It could be speculated that the canal termini in many of the 2°RCT cases may have been transported due to over-instrumentation and, therefore located further away from the radiographic apex compared to the previously untreated canals. Perhaps, given this complication, a direct comparison between flush root fillings in 1°RCT and 2°RCT cases may require different criteria, possibly facilitated by the use of electronic apex locators.

The effect of the quality of coronal restoration on 2°RCT (OR = 3.31; 95% CI: 1.07, 10.30) was similar to that on 1°RCT (OR = 1.82; 95% CI: 1.48, 2.25) (Ng *et al.* 2008) and supported by all three strands of evidence. The magnitude of the effect of coronal restoration on 2°RCT may have been over-estimated because of the small number of studies available but it may be inferred that coronal restorations fulfil a similar role in the two cases as the final stage of 2°RCT preventing re-infection of the root canal system.

In comparison with the gold standard, the evidence base for 2°RCT is weaker than that for 1°RCT. The pooled success rate of 2°RCT was approximately 77%, consistent with the findings for 1°RCT. Pre-operative periapical lesion, extrusion of root filling material, and unsatisfactory coronal restoration were all found to compromise the outcome of 2°RCT.

It may be concluded that according to the current best evidence, the primary goals of 2°RCT are to focus canal preparation on obtaining and maintaining access to the apical infection, achieving sufficient canal shaping to its terminus to facilitate adequate decontamination and then to provide a well condensed root filling extending to the canal system terminus without extrusion of any material. This should be followed as early as possible by the placement of a good quality coronal restoration to create a permanent (antibacterial) coronal seal.

In conclusion, the significant prognostic factors for 2°RCT identified from this review are similar to those for 1°RCT, strongly indicating that the principles and strategy for 2°RCT are identical to those for 1°RCT. The sole differences lie in the potentially compromised access to the said apical infection, either due to iatrogenic errors in canal preparation or inability to fully negotiate canal blockages due to natural or artificial materials. The outcome of 2°RCT should therefore be similar to 1°RCT as long as access to the apical infection can be re-established. There is therefore a need for clinicians to acquire the skill to diagnose and correct procedural errors as well as to prevent introduction of further iatrogenic errors during re-treatment. The acquisition of such skills must of necessity include the tactile skills necessary to manipulate stainless steel instruments back into previously patent (but now obstructed and deviated) canal termini. Nickel–titanium instruments, lacking the necessary physical properties to be appropriately pre-curved at the tip for re-direction, more-often-than-not prove unsuitable for the task. This may have important implications for training. These definitive observations are offered within the constraints of the limitations of the data available. There is still a palpable need for well designed prospective studies to evaluate the outcome of 1°RCT and 2°RCT at more detailed and sophisticated levels. In particular, there is a need to investigate the influence of numerous untested pre-operative prognostic factors specifically related to 2°RCT. Furthermore, it is imperative to carry out randomized controlled trials with sufficiently detailed data recording to establish optimal re-treatment protocols.

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Appendix IX

Meta-regression analyses to account for heterogeneity in analysing the effects of periapical status on the success rate of secondary root canal treatment

Covariate included	***tau*2**
(a) Comparison of teeth with or without periapical lesion	
None	0.2
Criteria for determination of success (strict or loose)	0.2
Unit of measure (root or tooth)	0.2
Geographic location of study (USA, Scandinavian or other countries)	0.3
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.3
Duration after treatment (≥4 years or not)	0.09
Decade of publication (before 70's, 1970-1989, 1990-2002)	<0.0001
(b) Comparison of teeth large or small periapical lesion	
None	0.01
Criteria for determination of success (strict or loose)	0.2
Unit of measure (root or tooth)	<0.0001
Geographic location of study (USA, Scandinavian or other countries)	0.3
Qualification of operator (specialist, postgraduate, undergraduate or GDP)	0.1
Duration after treatment (≥4 years or not)	<0.0001
Decade of publication (before 70's, 1970-1989, 1990-2002)	1.0

Appendix X

Success rates of primary and secondary root canal treatment stratified by each decade of age of patients in the prospective study

Age	Primary root canal treatment	Secondary root canal treatment
≤ 20	88.3%	79.6%
> 20 & ≤ 30	75.4%	75.3%
> 30 & ≤ 40	79.1%	81.1%
> 40 & ≤ 50	82.8%	82.9%
> 50 & ≤ 60	86.5%	78.2%
> 60 & ≤ 70	88.9%	77.0%
> 70	66.7%	77.3%

Appendix XI

Multivariable Cox regression model incorporating "type of treatment", "diabetic", "steroid therapy" and all the potential significant pre-, intra- & post-operative factors

Factors	HR	95% CI for HR*	P value
Type of treatment			
Primary root canal treatment	1		
Secondary root canal treatment	1.32	0.84, 2.08	0.2
Diabetic			
No	1		
Yes	3.23	1.24, 8.43	0.02
Systemic steroid therapy			
No	1		
Yes	3.09	0.97, 9.90	0.06
Pre-operative periodontal probing depth			
< 5mm	1		
≥ 5mm (narrow defects)	2.38	1.00, 5.69	0.05
Pre-operative pain			
No	1		
Yes	2.71	1.62, 4.54	< 0.0001
Pre-operative sinus			
No	1		
Yes	2.25	1.32, 3.86	0.003
Pre-operative cervical resorption			
No	1		
Yes	4.49	1.05, 19.18	0.04
Pre- or intra-operative perforation			
No	1		
Yes	3.88	1.71, 8.78	0.001
Patency at canal terminus			
No	1		
Yes	0.66	0.26, 1.68	0.38
Canal blockage during treatment			
No	1		
Yes	1.48	0.69, 3.16	0.31
Extrusion of gutta-percha root filling			
No	1		
Yes	1.95	1.13, 3.36	0.02
Cast post & core			
No	1		
Yes	2.68	1.19, 6.07	0.02
Post-operative temporary restoration present			
No	1		
Yes	8.50	3.82, 18.88	< 0.0001
Post-operative cast restoration present			
No	1		
Yes	0.39	0.24, 0.66	< 0.0001
Two proximal contacts			
No	1		
Yes	0.62	0.36, 1.09	0.10
Terminal tooth			
No	1		
Yes	1.16	0.51, 2.65	0.7

*Confidence interval for hazard ratio (HR) estimated using robust standard error to allow for clustering within patients